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Preface

Gary R. Lichtenstein, MD
Guest Editor

There have been numerous advances in the area of inflammatory bowel disease (IBD). IBD encompasses multisystem diseases of uncertain etiology. Since Drs. Crohn, Ginzburg, and Oppenheimer's initial description of Crohn's disease (CD) in 1932, and Drs. Wilks and Moxon's original description of ulcerative colitis (UC) in 1875, much has been learned about these two disorders. Both diseases occur worldwide–primarily in patients of young age (but they have been described in individuals who are young or old)–and spare no socioeconomic group. Recent scientific and technologic advances have led to a better comprehension of the pathogenesis that underlies these disorders and have enabled physicians and scientists to create better and more efficacious medical therapies for CD and UC. Medical therapies for IBD aim to induce and maintain disease remission; decrease disease-associated complications, including malnutrition, osteoporosis, and colon cancer; and ultimately, improve the patient's quality of life. In 1998, translational research confirmed infliximab's importance when this agent was approved for treatment of CD. Animal models and human data suggested that tumor necrosis factor-α was important for the inflammatory response in CD. This represented the introduction of biologics for the treatment of IBD.

This issue of the *Gastroenterology Clinics of North America* focuses on biologic therapy for the treatment of CD and UC. A highly distinguished group of sophisticated physician scientists has been assimilated to present an updated guide to the current status of selected foci in gastroenterology as related to the biologic therapy of IBD. The discussions range from laboratory-based findings to clinical pearls, taking us from the bench to the bedside. These articles highlight many of the advances to date and demonstrate the enthusiasm that is generated by current work in each area. This issue not only reviews the

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current state of the art, but also prepares you for the future. The subject matter is wide ranging, but not every area–as it relates to biologic therapy of IBD–is covered. As a result, this issue serves as a repository of the current basic and scientific knowledge for investigators in the field. We hope that we have supplied a review of the pertinent pathophysiology for the practicing physician/health care deliverer, and a clinical framework for assessment and treatment of patients who have IBD.

I am indebted to my fellow contributors for providing uniformly outstanding, detailed critical reviews amid their already busy schedules. My gratitude also is extended to Ms. Kerry Holland for her outstanding editorial assistance and her superb guidance in this issue. Lastly, I am most appreciative and extend thanks to all of my colleagues, patients, and those who have supported research in the field to help me uncover and extend the boundaries of my knowledge of IBD.

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Gastroenterol Clin N Am 35 (2006) xi
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ERRATUM

Hepatitis B: The Pathway to Recovery Through Treatment

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Please note that in the June 2006 issue of the *Gastroenterology Clinics of North America* (volume 35, number 2), the article "Hepatitis B: The Pathway to Recovery Through Treatment" by Drs. F. Blaine Hollinger and Daryl T.-Y. Lau was published without final edits due to a publisher's error. The complete, final version of the article is included as a special article in this issue (December 2006; volume 35, number 4).

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Biologics for Inflammatory Bowel Disease: Drug Approval and Monitoring in the United States

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THE STATUS OF BIOLOGICS FOR INFLAMMATORY BOWEL DISEASE

The first biologic for the treatment of inflammatory bowel disease (IBD), infliximab, was licensed by the US Food and Drug Administration (FDA) in August, 1998, for Crohn's disease (CD). Since then, biologics have been a primary focus for research and development of new treatments for IBD and other immune disorders [1]. The revenue for biologics for autoimmune diseases was estimated at $6.8 billion in 2003 and it is expected to grow to $11 billion by 2011 [2]. Two of the four most profitable biologics for autoimmune disease are used for IBD: infliximab, which was approved for ulcerative colitis in September of 2005 (it also is approved for CD, rheumatoid arthritis, psoriasis, and ankylosing spondylitis), and adalimumab, which is approved for rheumatoid arthritis, but not for CD, although it seems to be effective for CD in clinical trials. Several other biologics are in clinical trials in the United States. In January of 2006, the FDA noted a total of 18 active commercial investigational new drug applications (INDs) for biologics for ulcerative colitis or CD. As of June of 2006, the New Medicine Database listed all of the agents in clinical trials for IBD in the United States, including biologics [3]. There were 31 commercial INDs for CD and 18 commercial INDs for ulcerative colitis; the biologics make up a considerable portion of the current clinical research activity for IBD [3].

BIOLOGICS AND THE US FOOD AND DRUG ADMINISTRATION

US Food and Drug Administration Centers

The Biologics Control Act of 1902 gave the Federal Government authority to regulate the production and sale of biologic products, which at that time

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included vaccines and antitoxins. The Food, Drug, and Cosmetic Act of 1938 brought all drugs, including biologic products, under the purview of the FDA. The FDA defines biologics as medical products that are derived from living sources, including humans, animals, plants, or microorganisms [4].

In June of 2003, the FDA transferred some therapeutic biologic agents from the Center of Biologics Evaluation (CBER) to the Center for Drug Evaluation and Research (CDER) [5]. Those agents included monoclonal antibodies, cytokines, novel proteins, immunomodulators, and growth factors. Biologics that remain under the jurisdiction of CBER include cellular products, such as pancreatic islet cells, gene therapy products, vaccines, allergenic extracts, antitoxins, and blood components. CDER, which now oversees most of the biologics that are being used or tested for IBD, also regulates nonbiologic medications for IBD, so the approval process for most biologics for IBD is similar to the process for nonbiologics [5].

The Approval Process

FDA regulation of a new drug or biologic can be divided into three stages: the commercial IND, the new drug application (NDA), and postmarketing (phase 4) studies (Fig. 1) [6,7].

Before the investigational new drug application

During the preclinical testing of a new biologic agent, the sponsor accumulates data from short-term animal studies on the absorption, distribution, excretion, and toxicity of the agent. Data on genotoxicity, teratogenicity, and carcinogenicity are obtained from long-term animal studies [7]. The sponsor is invited to meet with the FDA to review the plans for testing, the progress, and whether a fast-track review process is appropriate for the agent when it is tested in

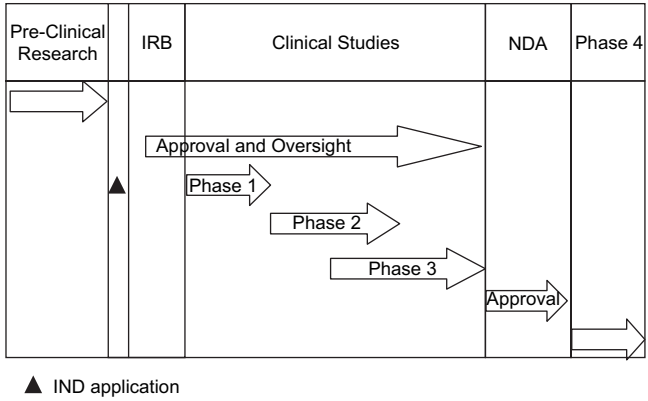

Fig. 1. Drug and biologics approval process. (*Adapted from* FDA center for Drug Evaluation and Research. Drug review and related activities in the United States. 2004 Online Training Seminar. Available at: http://www.connective.com/events/drugdev/; with permission.)

humans. The criterion for fast-track status is that the agent must have the potential to fulfill an unmet medical need for a serious or life-threatening disease [6].

The Investigational New Drug Application

An IND is not an application for approval to market a drug, but rather is a request for an exemption from the federal statute that prohibits shipment of unapproved drugs in interstate commerce [8]. An IND documents permission from the FDA to conduct human trials with a drug. In 2004, there were more than 15,000 active INDs for drugs, therapeutic biologics, and other biologics filed with CDER [7]. The long-term goal of a commercial IND is to gather data in support of an application for approval to market a drug or biologic. Noncommercial INDs include investigator-initiated INDs, which are for specific research proposals, and emergency use INDs and treatment INDs, which waive the usual approval process for conditions for which there are no other treatment alternatives. IND applications are evaluated by the FDA in 30 days; if submission is not rejected by the end of that time, the sponsor may proceed with clinical trials [9]. In the IND application, the sponsor must submit animal pharmacology and toxicology data, manufacturing data that document production procedures, stability, controls used for manufacturing the product, and the capability of producing adequate and consistent batches. In addition, the sponsor must submit clinical protocols and the qualifications of the proposed clinical investigators. Although not required, the sponsor also may choose to submit a confidential drug master file, with additional information on facilities, manufacturing processes, packaging, and storage. If the FDA notifies the sponsor of deficiencies in the IND that were not serious enough to prevent approval, the sponsor must correct the deficiencies while the clinical studies are underway [9].

Institutional Review Boards

Before research in humans may begin, the institutional review board (IRB) at each facility where subjects will be enrolled must approve all aspects of the clinical research, including the consent form. Each IRB is granted authority by the federal Office of Human Research Protection (OHRP) in a Federalwide Assurance for the institution. IRB approval and monitoring is required throughout all four phases of clinical trials. Each IRB reviews reports of unanticipated problems that occur in all studies using the same biologic, including studies at the IRB's own institution and at all others. IRBs also review reports from the data and safety monitoring boards for each study to decide if the study may continue, based on the interim safety reports. Each IRB is accountable to the OHRP to fulfill its responsibilities and is monitored by the Division of Compliance Oversight of the OHRP [10].

Clinical Trials: the Four Phases

Phase 1 studies are performed to determine the pharmacology, including metabolism and excretion, and the toxicity of an agent [7]. These studies are

conducted most commonly in groups (20–80 subjects) of healthy volunteers. Phase 1 studies also are performed in adults and children who have advanced malignancies for which there are no other clinical or research treatment options. Phase 1 testing may take 1 to 2 years. If the results of phase 1 testing are acceptable, phase 2 studies are performed in affected patients, usually 50 to 300, for proof of concept, assessment of different doses, safety, and preliminary data on efficacy. Phase 2 testing has taken up to 9 years for some drugs. If safety and some evidence for efficacy are demonstrated in phase 2 studies, then pivotal phase 3 studies are undertaken, with patient numbers from more than 100 up to 3000. Phase 3 studies determine the safety and efficacy of the agent at specific doses and frequency of administration. The data from phase 3 studies are used for the prescribing and package insert information. Phase 4 studies are performed after a drug is approved by the FDA and are mandated as a condition of approval. These studies investigate the use of the drug or agent for one or more of the following reasons: efficacy and safety for new patient populations, different doses, costs, long-term effects, and quality of life.

New Drug Application

The sponsor requests approval from the FDA of the new agent by way of an NDA [7]. Preclinical and clinical data are submitted, which includes chemistry, manufacturing, packaging, labeling, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, microbiology, and clinical safety and efficacy data. Case report forms are required for all of the study subjects. The NDA also contains patent information and certification. The NDA is reviewed at CDER by experts in microbiology, medicine, pharmacology, chemistry, and statistics. CDER also uses advisory committees for independent opinions and advice. Although the recommendations of the advisors are not binding, CDER's decision regarding approval usually, but not invariably, is in line with the recommendations. During the NDA review, CDER inspects the manufacturing facilities and clinical trial sites to verify the data and compliance with Current Good Manufacturing Practices. Samples of the drug or biologic are collected for analysis and verification in CDER laboratories. CDER also ensures that each statement for labeling of the drug is justified by the data. CDER has one of three options for a decision about the NDA: approval, approvable, or nonapprovable, with a final sign-off required from the CDER division director. Approval gives the sponsor permission to market the agent in the United States. If the decision was "approvable," the sponsor must satisfy conditions that are specified by the FDA, and the agent cannot be marketed until those conditions are met [8].

Accelerated Approval

Drugs or biologics that show exceptional promise for the treatment of serious conditions for which no current treatment exists are considered for accelerated approval. Surrogate end points, such as laboratory or imaging findings, are used to determine the safety and efficacy of an agent, rather than direct measurements of remission or survival. For example, natalizumab received

accelerated approval in November of 2004 for reducing the frequency of exacerbations in patients who have remitting-relapsing multiple sclerosis. At the time, natalizumab also was being tested in patients who had Crohn's disease. As a condition of approval, the FDA requires postmarketing studies to confirm safety and efficacy using direct clinical end points [6].

Orphan Drugs

Another potential route for approval of a biologic is as an orphan drug, defined by the FDA as an agent for the treatment of a rare disease that affects fewer than 200,000 Americans [11]. An agent also can be deemed an orphan drug if it used for a disease that affects more than 200,000 Americans, but there is no reasonable expectation that the cost of developing the treatment will be recovered by the sales of the drug in the United States. Potential avenues for orphan drug use in IBD include new treatments for pouchitis or microscopic colitis. Orphan drug approval is attractive to industry, because sponsors are granted 7 years of marketing exclusivity, and there is a 50% tax credit for expenses in clinical trials [12].

Postmarketing Surveillance

Within CDER, the Office of Drug Safety monitors adverse events through the Medwatch program, and receives more than 250,000 Medwatch reports per year [9,13]. Voluntary Medwatch reports are sent by health care professionals and consumers. It is mandatory for hospitals, nursing homes, importers, distributors, and manufacturers to submit Medwatch reports. The Office of Drug Safety is responsible for updating drug labeling, overseeing notification of the public about new risks, implementing or revising risk managements programs, and rarely, withdrawing approval of an agent. For example, the maker of natalizumab voluntarily suspended marketing in February of 2005, after two reported cases of progressive multifocal leukoencephalopathy [14]. In June of 2006, the FDA, through the Office of Drug Safety, granted approval of a supplemental Biologics License Application for resumption of marketing of adalimumab after revising the labeling with additional safety warnings, and introduction of a risk management plan [15].

WILL THERE BE GENERIC BIOLOGICS FOR INFLAMMATORY BOWEL DISEASE?

The charges that are incurred by the third-party payer for a year's treatment with infliximab were estimated to be as high as $72,000 [16]. Biologics for other diseases can be equally expensive. The high price of biologics may increase the pressure from consumers for the development of generics.

The Hatch-Waxman Act of 1984, known as the Drug Price Competition and Patent Term Restoration Act, encouraged marketing of generic drugs by shortening the drug approval process [17]. The Hatch-Waxman Act is an amendment to the Food, Drug, and Cosmetics Act that permits filing an Abbreviated NDA, in which generic manufacturers are not required to duplicate studies to demonstrate safety and efficacy of the new drug. Instead, the

generic manufacturer only must show bioequivalence of the generic and name brand product. Proving bioequivalence between biologics, however, is difficult, because physical and chemical characterization alone is not sufficient to show sameness [18]. Another hurdle for the development of generic biologics is that most currently used biologics were not approved under the Food, Drug and Cosmetics Act, but under the Public Health Service Act, which does not have a provision for generics [19]. Janet Woodcock, MD, director at CDER, noted in 2004 that, ". . .we do not believe that a protein could now be approved as a generic" [18].

There is the option for the FDA to reclassify biologics as drugs and then apply the Hatch-Waxman Act to the approval process for generics. To do this, the FDA would need to use safety and efficacy data from currently marketed biologics [19]. The manufacturers of these biologics argue that this action is unconstitutional, because it would amount to the FDA releasing trade secret data. Therefore, any attempts to bring forward a generic biologic could sink in legal quagmires, and new legislation may be necessary before generic biologics are approved.

SUMMARY

Biologics are a primary focus for research and development of new treatments for IBD and other immune disorders. CDER, which is a branch of the FDA, oversees most of the biologics that are being used or tested for IBD, and it regulates nonbiologic medications for IBD. The approval process for most biologics for IBD is similar to the process for nonbiologics. FDA regulation of a new drug or biologic can be divided into three stages: the commercial IND, the NDA, and postmarketing (phase 4) studies. It is unclear if generic versions of biologics can be approved within the current legislation.

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GASTROENTEROLOGY CLINICS
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Focus on Mechanisms of Inflammation in Inflammatory Bowel Disease Sites of Inhibition: Current and Future Therapies

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The advent of the anti–tumor necrosis factor (TNF) agent infliximab has dramatically changed the concept of treating refractory inflammatory bowel disease (IBD), particularly Crohn's disease (CD). Although infliximab has been proven to induce clinical response and remission with rapid onset, to spare steroids, to improve perianal disease, and to increase quality of life [1–4], there is a considerable unmet medical need in both CD and ulcerative colitis (UC) [11]. Twenty percent to 30% of patients who have refractory CD and 30% to 40% of those who have refractory UC do not respond to infliximab treatment. Moreover, the long-term use of this drug is associated with immunogenicity, which interferes with efficacy, and with the risk of infectious complications. Also, TNF is produced relatively late in the sequence of events involved in the inflammatory reaction and, considering the redundancy of immune pathways, the efficacy of infliximab has challenged immunologic paradigms. Therefore, the quest for novel biologic treatments continues. As a consequence, it has become a challenge for the clinicians to identify biologic agents that may enter clinical practice in the near future or at least have a fair chance of making it through the survival-of-the-fittest process known as clinical development. The ideal biologic agent for treating IBD should be aimed at an early event in the inflammatory cascade, selective without increasing morbidity and mortality, and devoid of immunogenicity to ensure sustained response over time. Although the initial trigger that unleashes the inflammatory cascade in CD and UC is unknown, recent advances in basic science have provided more insight into the pathophysiology of IBD. These evolving concepts have

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provided additional targets for drug development that eventually will open new perspectives for patients suffering from IBD (Table 1).

UNDERSTANDING THE INFLAMMATORY CASCADE IN INFLAMMATORY BOWEL DISEASE

Although the precise etiology of IBD has not been characterized, the most recent hypothesis concerning the underlying disease mechanism states that individuals who have a genetic predisposition, when confronted with unidentified aggressors from their natural environment, develop a loss of tolerance to luminal bacterial antigens and initiate an uncontrolled inflammatory reaction targeted at the bowel wall and at distant organ systems such as the joints, skin, or biliary tract (Fig. 1) [5]. Even though CD and UC are considered adaptive immune system–driven diseases, the quest for IBD-related genes has indicated that in some patients deficiencies in the innate immune response can be linked to the development of IBD. The first susceptibility gene identified in CD, *CARD15/NOD2* [6,7], is involved in the cytosolic recognition of bacterial cell wall components. The precise link between loss of the ability to sample bacterial antigens and the development of chronic intestinal inflammation has not been established. Nevertheless, mutations in genes encoding Toll-like receptors, membrane-bound bacterial wall sampling proteins, also have been associated with CD [8]. Finally, decreased expression of defensins, proteins synthesized as a defense against luminal bacteria, is associated with CD [9]. This growing body of evidence points toward a crucial role for defective innate

Table 1
Inflammatory pathways in inflammatory bowel disease targeted by biologic therapies

Target in inflammatory Reaction	Compound	Molecular Target	IBD Subtype	Development phase[a]
T-cell cytokines/ inflammatory pathways	adalimumab	TNF	CD	III
	certolizumab-pegol	TNF	CD	III
	fontolizumab	IFN-γ	CD	II
	MRA	IL-6 R	CD	II
T-cell differentiation/ proliferation	ABT-974	IL-12/23	CD	II
	CNTO-1275	IL-12/23	CD	II
	daclizumab	IL-2 R (CD25)	UC	II
	basiliximab	IL-2 R (CD25)	UC	II
	visilizumab	T-cell R (CD3)	UC/CD	II/III
Selective adhesion molecules	natalizumab	α_4 integrins	CD	III
	MLN-02	α_4 β_7 integrin	UC	III
Innate immunity/ mucosal repair	GM-CSF	unknown	CD	III
	EGF	unknown	UC	III

Abbreviations: CD, Crohn's disease; EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; R, receptor; TNF, tumor necrosis factor; UC, ulcerative colitis.

[a]Information on development phase is subject to change.

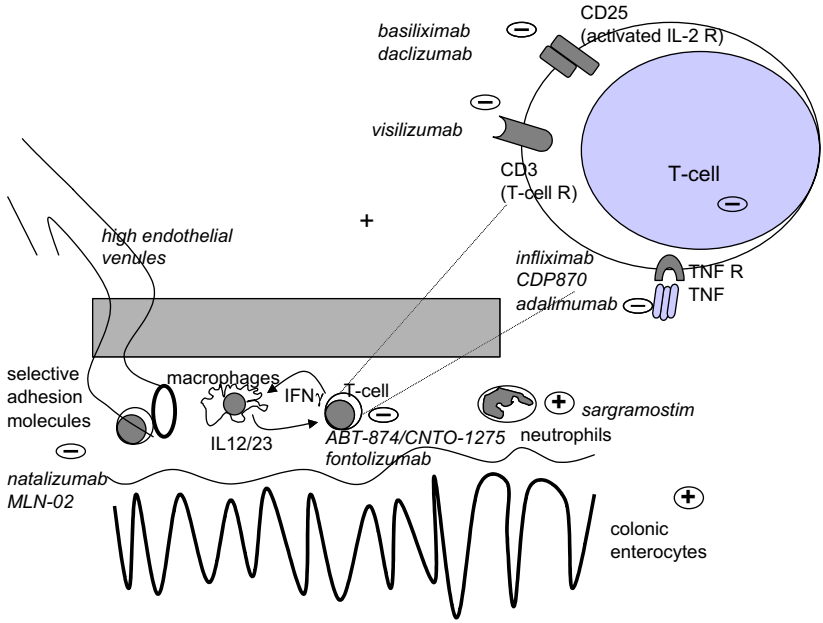

Fig. 1. Humanization of therapeutic antibodies. In general, the immunogenicity of therapeutic antibodies has decreased with advances in humanization. The efficacy of an antibody is determined by affinity, avidity, and antibody isotype, independent of the degree of humanization. C, constant region; CDR, complementarity-determining region; H, heavy chain; L, light chain; V, variable region.

immunity in early steps of the disease course, and boosting the innate immune system may have therapeutic potential.

Nevertheless, the crucial role of CD4+ T cells in the inflammatory cascade underlying IBD has been well established [5]. Activation of these T cells is a multistep process involving strict control by cytokines and membrane-bound cellular interaction. Naive T cells, which have matured in primary lymphoid organs, leave the blood stream to encounter antigen in the lamina propria. Depending on the activation of their antigen-specific T-cell receptor (CD3) on costimulatory molecules all present at the surface of antigen-presenting dendritic cells and on the local cytokine micromilieu, T cells differentiate in proinflammatory T-helper (Th) cells or in inflammation-controlling T-regulatory cells (T-regs). The activated Th cells in turn secrete proinflammatory cytokines that set off the T-cell and non–T-cell–mediated inflammatory response leading to IBD. The crosstalk between antigen-presenting dendritic cells and T cells is facilitated by a positive feedback loop involving the dendritic cell cytokines interleukin (IL)-12 and IL-23 and the T-cell cytokine interferon (IFN)-γ, respectively. Controlling this T-cell differentiation and activation at an early stage has been a major target for the development of biologic agents, as discussed later. Until recently, Th cells were mainly classified as Th1 or Th2 based on T-cell

phenotypes in mice and on cytokine profiles in humans. CD is associated with predominant Th1 activation, whereas the Th2 cell polarization in UC is more controversial. Recently, new Th subtypes have been discovered. In mice the Th17 cell is induced early in the inflammatory reaction in the presence of high local IL-23 and IL-6 levels [10]. Th17 cells promote the differentiation of Th1 and -2 cells and decrease the generation of counterinflammatory T-regs. Uncontrolled and permanent activation of Th17 cells may contribute to chronic bowel inflammation. Although the role of this cell in humans has not been clarified, it might be a selective target for future treatment strategies. To summarize the T-cell–centered paradigm, the uncontrolled inflammatory reaction in IBD is triggered by an imbalance between an excess of proinflammatory Th and effector T cells and a relative shortage of counterinflammatory T-regs. Induction of counterregulatory T-regs is an appealing therapeutic concept, and evidence for this mechanism has been found in rheumatoid arthritis. Most biologic treatments are believed to restore this imbalance either by preventing T-cell activation (eg, anti–IL-12, anti–IFN-γ, and anti-CD25 antibody) or by the induction of T-cell apoptosis (eg, anti TNF agents, anti-CD3 antibody). Induction of T-cell apoptosis is particularly desirable in CD because T cells of patients who have CD are refractory to apoptosis [5].

Therapies such as anti–IL-12/IL-23 or anti–IFN-γ agents that target early steps in the immune cascade may stop the inflammatory reaction before amplification steps occur. The immune system, however, is characterized by a high degree of redundancy: several parallel pathways induce similar downstream effects, and this redundancy could be a disadvantage in of inhibiting early steps. There also is redundancy in activating pathways further downstream, and the minority of patients who have CD and who initially do not respond to anti-TNF treatment may have a disease driven by other late cytokines such as IL-6.

Finally, as discussed in more detail later, immune cells are only temporary residents of the bowel wall and must be attracted to the site of action. This leukocyte trafficking is regulated by a complex interplay of adhesion molecules and has been successfully targeted to treat IBD.

BIOLOGIC THERAPIES: HOW DIFFERENT ARE THEY?

Several strategies are followed in drug development to improve the efficacy and tolerability of biologic agents. First, progress in protein engineering has eliminated immunogenic nonhuman peptide sequences from anti-human antibodies, a technique known as humanization [12]. Third-generation, humanized (± 95% human) antibodies and fourth-generation fully (100%) human antibodies usually are associated with less immunogenicity than seen in chimeric (75% human) monoclonal agents such as infliximab (Fig. 2). Also, subcutaneous administration eliminating the need for in-hospital infusions is the preferred method of drug administration for novel biologic agents. Finally, pathways in the immune reaction that do not directly involve TNF inhibition are being targeted. These combined strategies have created several compounds, mostly

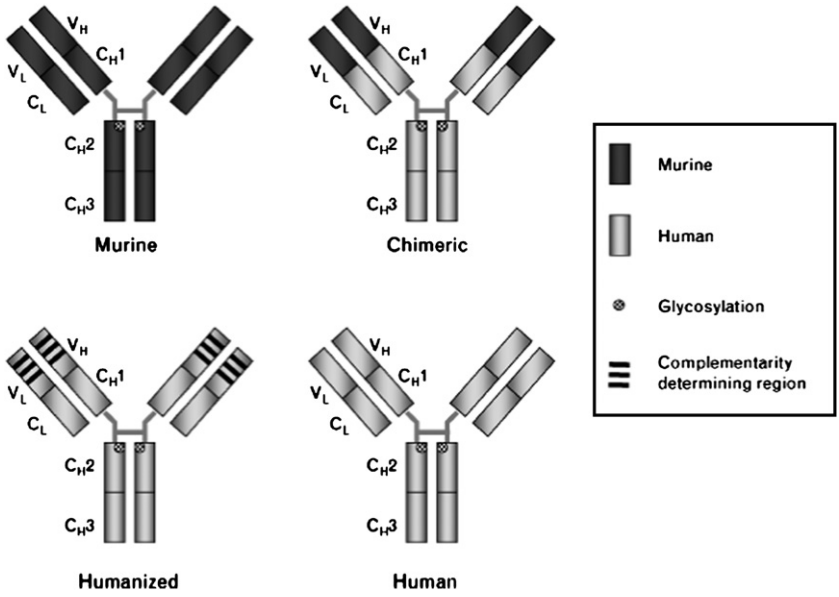

Fig. 2. The current concept on the inflammatory cascade, which underlies inflammatory bowel disease. IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; TNF R, tumor necrosis factor receptor.

monoclonal antibodies, that now are being tested for their potential in IBD treatment.

ANTI–TUMOR NECROSIS FACTOR STRATEGIES

The chimeric monoclonal anti-TNF IgG1 antibody infliximab has proven to be a highly efficacious induction and maintenance agent in patients who have refractory luminal and fistulizing CD [1–4]. Infliximab also induces rapid and profound endoscopic healing, improves quality of life, and may prevent hospitalizations and surgery [13].

The remaining mouse peptide regions in the chimeric protein are responsible for the formation of antibodies to infliximab. These anti-drug antibodies are associated with acute and delayed hypersensitivity reactions and with secondary loss of response [14,15]. Several treatment strategies, such as systematic maintenance therapy, concomitant immunosuppression, and prophylactic systemic steroids, decrease the incidence of formation of antibodies to infliximab [13–15]. Nevertheless, 20% to 30% of patients are unable to continue infliximab therapy because of unmanageable infusion reactions or loss of response. For these patients two more humanized compounds may restore disease control.

The fully human IgG1 antibody, adalimumab, is commercially available for the treatment of rheumatoid arthritis. Clinical efficacy in CD is inferred from open-label experience [16,17] and from data in controlled trials [18,19]. The

immunogenicity of this compound is limited (3% anti-drug antibodies with long-term use [19]).

Also, in two large placebo-controlled trials, certolizumab pegol or CDP-870, a humanized Fab antibody fragment binding TNF and linked to polyethylene glycol for subcutaneous administration, showed efficacy in patients who had refractory CD [20,21]. The molecular mechanism underlying the effect of anti-TNF agents in IBD is a matter of debate. Etanercept, a p75 TNF receptor construct, failed to show efficacy in a controlled trial for refractory CD [22]. This compound binds soluble TNF trimers but is not capable of inducing lysis of TNF-expressing cells. In rheumatoid arthritis, however, both etanercept and infliximab are clinically useful. In the last 5 years several in vitro and ex vivo studies have shown that infliximab induces apoptosis of T cells from patients who have CD [23–27]. Also, ex vivo experiments have shown that both infliximab and adalimumab induce caspase-dependent apoptosis in human lymphocytes [26,28,29]. Based on this evidence, it has been postulated that induction of T-cell apoptosis is the crucial mechanism of action for anti-TNF agents in IBD. Additional evidence for this hypothesis has been inferred from pharmacogenetics. Patients who had mutations in genes encoding Fas-ligand and caspace-9, crucial steps in apoptosis, were found to have a decreased likelihood of response to infliximab [30]. Recently, however, some doubt has been cast on the crucial role of T-cell apoptosis in ensuring the effect of anti-TNF agents in IBD. First, certolizumab does not seem to induce T-cell apoptosis despite its clinical efficacy in CD. Second, T cells of patients who have UC are not resistant to apoptosis, as is the case in CD, where restoration of T-cell apoptosis seems a more logical target for biologic agents. Further research is necessary to clarify this issue.

In addition to the neutralization of soluble or membrane-bound TNF and the induction of cell lysis or apoptosis, other mechanisms may contribute to the activity of anti-TNF agents. Infliximab induces reverse signaling through membrane-bound TNF, shutting down intracellular signaling pathways [27,31]. TNF reduces the function and possibly the proliferation of CD4+/CD25+ T-regs in patients who have rheumatoid arthritis [32,33]. Infliximab has been shown to restore this functional deficit reflected in an increased expression of FoxP3, a specific marker of T-reg activation, and in an increase in the suppressive activity of CD4+/CD25+ T cells [33,34]. Finally, infliximab restores the leaky gut barrier in patients who have active CD, although it is unclear whether this restoration is a primary effect or a consequence of epithelial repair [35,36].

SELECTIVE ADHESION MOLECULE–INHIBITING AGENTS

To patrol antigens in the gut lumen and to assist in intestinal inflammatory reactions, leukocytes need to be directed toward the gastrointestinal tract. The journey of T cells from the blood to antigen-rich organs such as the gut or the lungs is guided by an elaborate system of traffic signals or adhesion molecules [37]. To encounter antigen and to engage in tissue inflammation, leukocytes must leave the primary lymphoid organs and the blood stream.

Blood-borne cells engage with the endothelium of postcapillary vessels, the high endothelial venules, before they migrate into the tissue [37]. This interaction is hindered by the high relative speed at which leukocytes travel, creating an important shear stress in the blood stream. A highly effective and sequential adhesion system has emerged to overcome these physical forces. Selectin bonds provide a high tensile strength but are short lived, and the T cell rolls over the endothelium from one selectin bond to the next. Secondary adhesion molecules, all members of the integrin family, definitively stop the lymphocytes to allow migration. The humanized antibodies antegren (IgG4) and mLN-02 (IgG1), targeted at α_4-integrins, have entered clinical trials in both CD and UC [38–40]. $\alpha_4\beta_1$-integrin binds to vascular cell adhesion molecule 1, and $\alpha_4\beta_7$-integrin binds to mucosal addressin cell adhesion molecule 1 (MadCAM-1) [41]. MadCAM-1 typically is associated with murine Peyer's patches and also with human gut–associated lymphoid tissue [42]. Even if T-cell migration into the inflamed bowel segments is of paramount importance in IBD pathogenesis, a decreased exit of lymphocytes from the mucosa and an increased local activation or proliferation also may be mechanisms by which integrins perpetuate the inflammatory reaction in IBD. There is some evidence supporting a role for adhesion molecules in interactions between T cells and resident dendritic cells or mesenchymal cells in the intestinal mucosa and submucosa. The extracellular matrix protein, fibronectin, for instance, is an $\alpha_4\beta_7$ integrin ligand [43], and this interaction may influence the function of stromal cells, such as antigen-presenting dendritic cells or fibroblasts. Other extravascular ligands for α4 integrins include matrix molecules such as osteopontin and thrombospondin and ADAM28, a metalloprotease domain constitutively expressed on lymphocytes [44]. Intracellular adhesion molecule 1 and α4-integrin binding to their respective addressins induces a costimulatory signal in antigen presentation to T cells inducing lymphocyte proliferation and cytokine production [43]. Antegren has shown activity, particularly in maintenance treatment of patients with CD [38,39]. Unexpected toxicity with the occurrence of progressive multifocal leukoencephalopathy, a devastating brain disorder caused by JC virus, in one patient who had CD and in two patients who had multiple sclerosis has halted further development in IBD until more data are available on the real risk for this lethal complication in the IBD population [45–47]. mLN-02 is effective in the treatment of moderate UC, but this humanized antibody seems to induce neutralizing anti-drug antibodies [40].

ANTI–IL-12/IL-23 P40 AND ANTI–GAMMA INTERFERON ANTIBODIES

IL-12 and IL-23, two related cytokines sharing a common p40 subunit, are crucial in an early phase of the inflammatory reaction driving CD. These cytokines create a positive feedback loop of crosstalk between T cells and macrophages, also involving IFN-γ, which eventually leads to secretion of TNF by both cell types. Inhibiting this feedback loop would shut down the inflammation before TNF-mediated effects can occur.

All trials targeting this pathway have been conducted in moderately active CD. The IL-12/IL-23 p40 subunit is targeted by ABT-874 (Abbott) and CNTO-1275 (Centocor), both fully human IgG1 monoclonals. A phase II study of SC ABT-874 at doses of 1 mg/kg and 3 mg/kg for 7 weeks in 79 patients who had active CD demonstrated efficacy for induction of response and remission in the group receiving the higher dose [48]. A higher proportion of actively treated patients experienced injection-site reactions, and 3 of 79 patients developed anti-drug antibodies that interfered with drug levels in two patients. CNTO-1275 has just entered clinical trials. The relative importance of blocking IL-12 or IL-23, both targeted by ABT-874 and CNTO-1275, for the efficacy of these biologic agents is at present not entirely clear.

Fontolizumab is a humanized IgG1 monoclonal antibody against IFN-γ. A phase II study of intravenous fontolizumab at doses of 4 mg/kg and 10 mg/kg at week 0 in 133 patients who had active CD failed to achieve the primary end point of response at week 4. A subgroup analysis demonstrated efficacy in patients who had elevated baseline concentrations of C-reactive protein who received a second dose of fontolizumab at week 4 [49,50]. The safety of maintenance treatment with reported doses is being explored currently in an open-label trial.

ANTI-CD3 ANTIBODIES

The interest in anti-CD3 antibodies as powerful immunosuppressive agents is not new. More than a decade ago OKT3, a mouse monoclonal antibody specifically targeted at the human CD3 complex on T cells, was introduced in the clinic in anti-rejection regimens for solid-organ transplantation. As has been the case for every murine monoclonal antibody, the clinical application of this antibody has been limited by the induction of neutralizing anti-murine antibodies. Moreover, OKT3 induces a severe cytokine-release syndrome caused by T-cell activation. This activation results from OKT3-mediated crosslinking of CD3-expressing T cells and Fc receptor–bearing cells. Even if the cytokines and immune pathways underlying UC are still incompletely characterized, there is a rationale for eliminating activated lymphocytes as a therapeutic strategy in this immune-mediated disease.

Protein Design Labs (Fremont, California) developed a mouse monoclonal antibody, M291, which competes with OKT3 for binding CD3-expressing cells. Based on this antibody, a humanized non–Fc receptor–binding antibody, huM291, was engineered, and this compound has been tested in UC [51]. Visilizumab potently induces apoptosis of activated T cells without activating resting T cells. An open-label pilot trial enrolling 24 patients who had severe UC suggested clinical efficacy, with 66% remission and 87% response. Also clear endoscopic improvement was noted [52]. Further dose-finding controlled trials are ongoing, and more than 100 patients have been enrolled. The temporary T-cell depletion and reactivation of Epstein-Barr virus replication observed with visilizumab is somewhat surprising, because only activated lymphocytes are a target for the antibody, and even in severely active UC only a minority of the total T-cell population is

activated. Therefore, temporary changes in T-cell trafficking or function may contribute to T-cell depletion and should be explored further.

ANTI-CD25 ANTIBODIES

The efficacy of medical immunosuppression with cyclosporine in the treatment of severe UC has been clearly established [53,54]. The macrolide compounds cyclosporine and tacrolimus reduce lymphocyte activation and proliferation by inhibiting IL-2 synthesis through the inhibition of the calcineurin pathway. IL-2 interacts with specific receptors on the T-lymphocyte membrane to induce a clonal expansion of T-effector cells [55]. The role of the activated IL-2 receptor (CD25) in UC is somewhat controversial, because it has been shown that IL-2 cytokine or IL-2 receptor knockouts develop spontaneous colitis [56–58]. Indeed, T-regs, a subclass of lymphocytes directed at controlling exaggerated immune responses, are CD25+/CD4+. Therefore, inhibition of CD25 theoretically may reduce the inflammatory reaction but also may unleash uncontrolled inflammation [58]. Recently, humanized monoclonal antibodies that neutralize the binding capacity of the high-affinity IL-2 receptor CD25 on antigen-exposed T lymphocytes have been developed. These antibodies have been registered in the prevention of acute renal transplant rejection [59–61]. Ample clinical trial evidence has been gathered in psoriasis, uveitis, and asthma as well as in solid-organ transplantation. Protein Design Labs developed daclizumab, a humanized monoclonal antibody of the human IgG1 isotype [62]. Novartis developed a chimeric anti-CD25 monoclonal IgG1 antibody, basiliximab [61]. Both antibodies have been tested in open-label trials for active UC [63,64]. Although the two trials suggested therapeutic potential for both compounds, a recent placebo-controlled trial with daclizumab failed to show efficacy [65] despite long-lasting peripheral CD25 saturation. This experience suggests that controlled data are needed for basiliximab also.

ANTI–INTERLEUKIN-6 RECEPTOR ANTIBODIES

MRA, a humanized monoclonal antibody against the interleukin 6 receptor, has shown efficacy in a phase II study for active CD at doses of 8 mg/kg intravenously every 2 weeks or every 4 weeks through week 12 in 36 patients who had active CD. Both induction of response and remission were higher in the group treated every 2 weeks [66]. As discussed previously, this antibody may be particularly useful for patients refractory to anti-TNF agents, although in the trial by Ito and colleagues [66] none of the patients were refractory to anti-TNF treatment.

AGENTS PROMOTING INTESTINAL REPAIR AND THE INNATE IMMUNE SYSTEM

As discussed previously, restoring the epithelial barrier may be one of the beneficial effects of anti-TNF therapies, but epithelial growth factors (EGF) are direct promoters of mucosal repair and restitution [68]. Several growth factors have been evaluated, predominantly in UC. Unlike CD, UC is essentially a mucosal disease, and the extent of mucosal ulcerations determines the severity of the disease.

Several growth factors, such as trefoil factor, transforming growth factor-β, keratinocyte growth factor (KGF), and EGF, have been implicated in the preservation of mucosal integrity and the regeneration of damaged mucosa [67]. Repifermin, KGF-2, was not effective in a placebo-controlled trial that included 88 patients who had moderately active UC [68]. EGF formulated as an enema has been used in a smaller placebo-controlled trial to treat mild-to-moderate UC in combination with oral mesalamine [69]. Twenty-four patients were randomly assigned (1:1) to receive placebo (100-mL inert enema) or EGF (5 μg in 100-mL enemas). After 2 weeks of treatment as many as 83% of actively treated patients (10/12) achieved disease remission, versus 8% of placebo recipients (1/12). This remission was sustained in all patients through week 4 and started to wear off after 8 to 12 weeks.

Growth factors might be employed to restore the mucosal barrier and also could be targeted at boosting the cellular components of the innate immune system such as neutrophils and macrophages, enabling them to eliminate antigens before they can trigger the adaptive immune response. In chronic granulomatous disease, glycogen storage disease, and Chediak-Higashi syndrome, disorders characterized by neutrophil dysfunction, transmural enterocolitis develops, and these patients respond to stimulation of the innate immune system through treatment with sargramostim (recombinant granulocyte macrophage colony-stimulating factor). A phase II study of subcutaneous sargramostim at a dose of 6 μg/kg/d for 8 weeks in 124 patients who had active CD failed to demonstrate efficacy for the primary end point of clinical response, although the drug showed efficacy for the secondary end point of remission. The precise mechanism of action of the pleiotropic growth factor sargramostim in IBD has not been elucidated fully, but it undoubtedly affects bone marrow myelopoiesis, because bone pain is a specific side effect of this treatment [70].

SUMMARY

Anti-TNF antibodies were the first biologic agents registered to treat patients who have CD and, more recently, patients who have UC. The sequence of events underlying the inflammatory reaction in IBD is extremely complex, however, and involves both the innate and antigen-driven adaptive immune system. Novel therapies are directed at several key players of this cascade. Blockade of T-cell proliferation and activation and inhibition of T-cell cytokines has been most extensively targeted by clinical trials in humans. Inhibition of adhesion molecules and the use of selected growth factors seem to have therapeutic potential. Restoration of regulatory T-cell and dendritic-cell function is still waiting to be explored in clinical trials. Although an increasing number of biologic therapies for IBD are being developed, the discovery of the full spectrum of treatment modalities is only beginning. Often, however, the clinical efficacy of biologic agents is investigated, and for some molecules is established, before mechanisms of action are specifically explored. Eight years after the Food and Drug Administration approved infliximab for the treatment of luminal CD, it is not known how this anti-TNF antibody actually dampens inflammation in IBD. The advent of newer anti-TNF agents is only postponing the answer.

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GASTROENTEROLOGY CLINICS
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General Principles and Pharmacology of Biologics in Inflammatory Bowel Disease

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Since the Food and Drug Administration approved the first biologic agent, infliximab, to treat Crohn's disease (CD) in 1998, additional biologic strategies targeting tumor necrosis factor (TNF) and other proinflammatory targets are being evaluated for use in inflammatory bowel disease (IBD). This article reviews the pharmacology and immunogenicity of the anti-TNF therapies including infliximab, adalimumab, and certolizumab; selective adhesion molecule inhibitors including natalizumab and MLN02; and the CD3 receptor inhibitor, visilizumab.

ANTI–TUMOR NECROSIS FACTOR-α MEDICATIONS

Tumor Necrosis Factor-α: Structure and Physiology

TNF-α is a 51-kd trimer cytokine, formed by the combination of three inactive soluble 17-kd monomer proteins, which are secreted by monocytes, macrophages, and T cells [1,2]. The gene encoding these monomers is located on the short arm of chromosome 6 within the major histocompatibility complex [3]. TNF-α trimers bind with similar affinity to two receptors (55-kd and 75-kd proteins, also known as TNF-R1 and TNF-R2, respectively). Binding of TNF-α to TNF-R1 results in a series of intracellular events that culminates in the activation of two major transcription factors, nuclear factor κB and c-Jun, which induce genes responsible for a wide range of biologic activities including cell growth and death, development, oncogenesis, immune, inflammatory, and stress responses (Fig. 1) [4]. Additionally, both receptor types may be proteolytically cleaved to release soluble binding protein, which binds to circulating TNF-α and may either neutralize or increase its activity [5–7].

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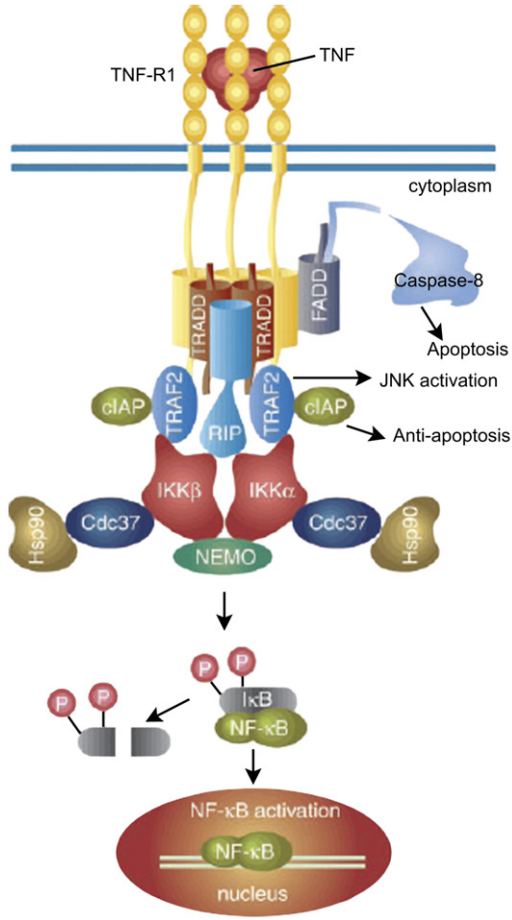

Fig. 1. TNF signal transduction pathway. Engagement of TNF with its cognate receptor TNF-R1 results in the release of SODD and formations of a receptor-proximal complex containing the important adaptor proteins TRADD, TRAF2, RIP, and FADD. These adaptor proteins in turn recruit additional key pathway-specific enzymes (eg, caspase-8 and IKKβ) to the TNF-R1 complex, where they become activated and initiate downstream events leading to apoptosis, NF-κB activation, and JNK activation. (*From* Chen G, Goeddel DV. TNF-R1 signaling: a beautiful pathway. Science 2002;296:1634–5; with permission. Available at: www.sciencemag.com. © Copyright 2002 AAAS.

Role of Tumor Necrosis Factor-α in Inflammatory Bowel Disease

TNF-α mediates multiple proinflammatory changes that play a central role in the pathogenesis of IBD, including neutrophil recruitment to local sites of inflammation, activation of both coagulation and fibrinolysis, and induction of granuloma formation [8]. Further, increased numbers of TNF-α–producing cells are present from intestinal biopsy specimens in children with both IBD (CD more frequently than ulcerative colitis [UC]) and nonspecific

inflammation, compared with those without inflammation [9]. Moreover, enhanced secretion of TNF-α from lamina propria mononuclear cells has been found in the intestinal mucosa of IBD patients and correlates with degree of inflammation [10]. In patients with CD, TNF-α–positive cells have been found deeper in the lamina propria and in the submucosa, whereas TNF-α immunoreactivity in UC was located predominantly in subepithelial macrophages [11]. Additionally, there may be insufficient increased release of soluble TNF receptor from lamina propria mononuclear cells of patients with IBD in response to enhanced secretion of TNF-α [12]. Increased levels of TNF-α in the stool have also been found from children with active IBD [13]. Elevated levels of TNF-α have been found in the serum of children with active UC and colonic CD [14], but another study did not find differences in TNF-α levels between children with IBD and those with IBS [15]. TNF-α may act as a cofactor for Th1 cell response, and treatment with an anti-TNF agent has been shown to down-regulate other Th1 cytokines in addition to TNF [16].

Whereas TNF-α is believed to play an integral role in the pathogenesis of IBD and other inflammatory diseases, such as rheumatoid arthritis (RA) and psoriasis, absence of TNF-α may increase susceptibility to infection such that anti–TNF-α agents must be targeted to decrease TNF-α levels to normal but not to below physiologic levels [17].

INFLIXIMAB

Structure and Mechanism of Action

Infliximab (Remicade; Centocor, Malvern, Pennsylvania) is a monoclonal chimeric antibody, targeting human TNF-α, composed of a human constant region $IgG_1\kappa$ light chain, accounting for approximately 75% of the antibody, linked to a mouse variable region [18]. Infliximab binds to the transmembrane and soluble form of TNF-α [18,19], paradoxically increasing its half-life, but decreasing its activity [20]. Infliximab is specific to TNF-α and does not bind TNF-β (lymphotoxin α) [21]. In vitro, infliximab also promotes complement fixation and antibody-dependent cytotoxicity of $TNF\text{-}\alpha^+$ cells including activated $CD4^+$ T cells and macrophages [19].

Pharmacodynamics

In vivo, infliximab reduces histologic inflammation. After a single infusion in patients with steroid-refractory ileocolonic CD almost no neutrophils could be detected and there was also a decrease in mononuclear cells; aberrant colonic epithelial HLA-DR expression completely disappeared; and the percentage of intercellular adhesion molecule 1, lymphocyte function-associated antigen 1–expressing and interleukin 4– and TNF-positive lamina propria mononuclear cells sharply decreased [22]. As reviewed by Bell and Kamm [23], infliximab also decreases proinflammatory cytokines interleukin-1 and -6 and adhesion molecules E-selectin and intercellular adhesion molecule-1. In RA, infliximab has been demonstrated to reduce serum levels of matrix metalloproteinase 1 and 3 [24], and to induce T-cell apoptosis in vitro [25].

Pharmacokinetics

Data regarding the pharmacokinetics of infliximab in IBD are derived primarily from one study of single intravenous infusions of 5, 10, or 20 mg/kg given to patients with moderate to severe CD [20,26]. There is a linear relationship between the administered dose and the maximum serum concentration (C_{max}) and the area under the concentration-time curve. The volume of distribution at steady state (V_d) and clearance are independent of dose. Infliximab is primarily distributed within the vascular space and has a prolonged half-life ($T_{1/2}$) (for 5 mg/kg: median = 7.7–9.5 days) [20,26]. Repeated infusions at 0, 2, and 6 weeks showed predictable concentration-time profiles, and no systemic accumulation of infliximab with maintenance dosing has been demonstrated [26]. While no significant differences in clearance or volume of distribution have been seen when patients are stratified by age, weight or gender, antibodies to infliximab increase the rate of clearance [26].

In the ACCENT I trial, 573 patients all received one dose of infliximab, 5 mg/kg, and were then randomized to receive either placebo at 2 and 6 weeks and thereafter every 8 weeks until week 46, or 5 mg/kg on the same schedule, or 10 mg/kg administered every 8 weeks after completing induction with 5 mg/kg: by week 14 serum infliximab concentrations were undetectable in more than 50% of patients who received placebo after only one 5 mg/kg dose of infliximab. Although the 10 mg/kg group had higher trough concentrations after week 22, trough concentrations remained relatively constant up to week 54 in the patients who received maintenance with either 5 or 10 mg/kg, indicating that the drug did not accumulate [27].

In another study evaluating repeated dosing of 10 mg/kg every 8 weeks for four doses in 73 patients with moderate to severe CD, stable serum concentrations were seen, and most patients still had detectable concentrations of infliximab 12 weeks after the final infusion (median 2.2 μg/mL) [28].

Methotrexate prolongs both the duration of response and the clearance of infliximab in patients with RA given infliximab at 1 mg/kg, but this effect was not demonstrated with higher doses. This synergy was postulated to reflect higher rates of antibody formation in the low-dose infliximab group [29].

There also seems to be a drug interaction between azathioprine and infliximab: a significant increase in mean 6-thioguanine nucleotide level was seen 1 to 3 weeks after the first infusion of infliximab in 32 patients with CD taking concomitant azathioprine compared with baseline (442 versus 277 pmol/8 × 10 [8], respectively, $P < .001$); mean 6-thioguanine nucleotide levels returned to preinfliximab levels at 3 months after the first infusion. A parallel decrease in leukocyte count and increase in mean corpuscular volume were also observed. Further, patients with a response to infliximab had a significantly higher mean 6-thioguanine nucleotide level than those who did not (478 versus 257, $P < .01$) [30]. Although the exact nature of the interaction between azathioprine and infliximab has not been elucidated, it has been postulated that infliximab may increase absorption of azathioprine or decrease the clearance by improving endothelial function or, less likely, by inhibiting thiopurine methyltransferase

inhibition. In patients who were in remission after 6 months of treatment with infliximab, discontinuation of immunomodulator therapy (azathioprine or methotrexate) did not affect efficacy at 1 year despite decreased trough levels compared with patients who continued immunomodulator therapy [31].

Immunogenicity

Although less immunogenic than a 100% murine antibody, chimeric antibodies are recognized as foreign antigens by the human immune system that may respond by creating antibodies to various sites on the molecule [32]. The rate of antibody formation to infliximab is reportedly 6% to 61%; this wide range may be attributed to different dosing schedules, concomitant immunomodulator therapy, and variations in cutoffs for titer values. Antibodies to infliximab (ATI) are also known as human antichimeric antibodies or HACA [32].

ATIs are important for two reasons. First, they have been associated with lower serum drug concentration levels [33] that translate into decreased or shortened duration of efficacy [33,34]. In patients with luminal or fistulizing CD ($n = 125$) treated with infliximab at 0, 2, and 6 weeks, and then retreated on relapse, ATI were detected in 61% of patients. In those with ATI concentration ≥ 8 μg/mL (37%) compared with those <8 μg/mL, the median duration of response was 35 days as compared with 71 days ($P < .001$) [33]. In the observational part of another trial in which 53 patients with CD received a total of 199 infusions of infliximab (5 mg/kg), 73% who lost response to therapy were positive for ATI, compared with 0 of 21 continuous responders ($P < .0001$) [34]. ATI positivity did not affect outcome at 1 year in patients receiving maintenance dose infusions in the ACCENT I trial, likely because of a large proportion of patients who were "indeterminate" for ATI production. In those who lost response, increasing the dose was effective in 80% to 90% of cases [35].

The second impact of antibodies to infliximab is an increased risk of acute and delayed transfusion reactions [33,34]. In a study by Baert and coworkers [33], a higher risk of an infusion reaction was seen in patients with antibody titers ≥ 8 μg/mL (relative risk = 2.4, $P < .001$). Similarly, patients who were positive for ATI in the study by Farrell and coworkers [34] were found to have a significantly higher incidence of infusion reactions compared with ATI-negative patients (40% versus 4.7%, $P = .0001$). Although the presence of ATIs is associated with an increased frequency of acute infusion reactions and delayed hypersensitivity reactions [36], most ATI-positive patients do not experience an adverse event after retreatment with infliximab. ATI should not be routinely tested in the absence of loss of response or an infusion reaction, because a positive result in and of itself does not change management [36].

A commercial assay for ATI measures both antimurine antibodies to epitopes on the variable region of infliximab, and antiallotypic antibodies to the human IgG_1 constant region [32]. When this assay has been tested in patients receiving infliximab, however, only antimurine antibodies were found [37]. Of

note, the presence of infliximab in the serum interferes with the assay, and ATI cannot be measured with detectable levels of infliximab. When an assay is negative for ATI but infliximab levels are detectable, it is traditionally considered indeterminate, although some view this as a negative result because the presence of chimeric (or human) target antibodies interferes with assays for antichimeric (or human) antibodies [37].

The development of ATI can be reduced by several means. First, high-dose induction [38] and maintenance therapy, in contrast to episodic administration, has been shown to decrease the rate of antibody formation. The group of patients who received only one dose of infliximab and, thereafter, placebo in the ACCENT I trial had a higher rate of antibody formation (28%) compared with those who received maintenance infusions at 5 or 10 mg/kg (9% and 6%, respectively) [27]. In another study, receiving a second dose of infliximab within 8 weeks of the first was significantly protective against the formation of antibodies [34].

Second, concomitant use of steroids or immunomodulators is associated with a decreased rate of antibody formation. The use of low-dose methotrexate (7.5 mg/wk) in patients with RA was protective against the formation of ATI, particularly at lower doses of infliximab. This effect seems to translate to clinical response: when methotrexate was used in conjunction with infliximab, 1 mg/kg, the median duration of response increased from 2.6 to 16.5 weeks (20% response) or 12.2 weeks (50% response) in more than 60% of patients ($P = .006$ and $P = .002$, respectively). This synergy was not apparent at higher doses of infliximab (3 or 10 mg/kg) [29]. In ACCENT I, 6% of patients receiving steroids and immunomodulators at baseline developed antibodies compared with 17% receiving steroids alone, 10% receiving immunomodulators alone, or 18% receiving neither [27]. Similar findings were observed in patients enrolled in the ACCENT II trial where those receiving steroids (13%), immunodulators (11%), or both (4%) were less likely to develop antibodies than those not taking steroids or immunosuppressants at baseline (24%) [39]. In the study by Baert and coworkers [33], 43% of patients taking immunosuppressive agents developed ATIs compared with 75% of patients not taking these medications ($P < .01$); further, median antibody titers were lower in patients receiving concomitant immunomodulator therapy (13.8–21.4 μg/mL versus 1.3–1.5 μg/mL). Farrell and coworkers [34] also found that concurrent immunosuppressant therapy with the first infliximab infusion in 53 patients with CD was associated with decreased ATI formation (24% versus 63%; $P = .007$).

Finally, pretreatment with hydrocortisone may reduce the risk of ATI formation. As demonstrated by Farrell and coworkers [34], 26% of CD patients pretreated with 200 mg of intravenous hydrocortisone before infliximab infusions developed ATI 16 weeks postinfusion, compared with 42% of those given placebo ($P = .06$). Pretreatment also correlated with nonsignificant improvement in clinical response, remission rates, and fewer infusion reactions. These effects may have been dampened by the concomitant use of immunomodulators in the

placebo group [34]. Gender, location of disease, and smoking status do not seem to correlate with development of ATI [33].

ADALIMUMAB

Structure and Mechanism of Action

Adalimumab (D2E7, Humira; Abbott Laboratories, Chicago, Illinois) is a subcutaneously administered recombinant human IgG_1 monoclonal antibody targeted to human TNF-α. It consists of human-derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab binds with high specificity and affinity to TNF-α, blocking its interaction with p55 and p75 receptors and, similar to infliximab, does not bind to lymphotoxin (TNF-β). In vitro, adalimumab also lyses surface TNF-expressing cells in the presence of complement [40] and induces monocyte apoptosis [41]. Although at the time of this writing adalimumab has Food and Drug Administration approval for treatment of moderate to severe RA and psoriatic arthritis, approval for CD is anticipated.

Pharmacodynamics and Efficacy in Inflammatory Bowel Disease

Initially, two open label trials suggested efficacy in patients who had lost response to infliximab [42,43], followed by the larger CLASSIC I and II double-blind, randomized trials that demonstrated effectiveness over placebo in induction and maintenance of remission, respectively, in anti–TNF-naive patients with CD [44,45].

Pharmacokinetics

In the CLASSIC I trial, mean serum concentrations (micrometer per milliliter) of adalimumab at week 4 followed a linear pattern: 2.79 ± 1.48 ($n = 66$), 5.65 ± 3.06 ($n = 65$), and 12.61 ± 5.25 ($n = 67$) for the 40/20-mg, 80/40-mg, and 160/80-mg groups, respectively. Similarly, a linear dose-response was demonstrated across the three groups at week 4 for the end points of both clinical remission and response [44]. Although no differences in mean serum concentrations were observed with concomitant 6-mercaptopurine or azathioprine in the CLASSIC I trial [44], concomitant administration of methotrexate increases the mean steady-state trough concentrations from 5, to 8 to 9 μg/mL in patients with RA [40]. In CLASSIC II, mean serum adalimumab concentrations were higher in those receiving 40 mg weekly compared with every other week. Although serum concentrations in the placebo group were measurable through week 24, concentrations fell to zero by week 56. The median clearance was 14.9 mL/h; concomitant azathioprine or 6-mercaptopurine slightly lowered or had no effect on clearance. Although the effect of methotrexate on clearance could not be determined ($n = 6$), the overall median clearance of adalimumab in this study was comparable with that in RA patients treated with concomitant methotrexate. Adalimumab seems to reside predominantly in the extracellular space [46].

Bioavailability of adalimumab has been estimated at 64% in healthy volunteers, and $T_{1/2}$ was approximately 2 weeks. There was a trend toward increased rate of clearance in the presence of antiadalimumab antibodies (AAA) and a decreased clearance rate in older patients (40–75 years). After

correction for weight, no gender differences have been observed, and healthy volunteers and patients with RA displayed similar, overall, pharmacokinetics [40].

Immunogenicity

In the CLASSIC-II study, 2.6% (7 of 269 patients) developed AAA, also known as human antihuman antibodies (HAHA); one patient who developed AAA was in the placebo group. Of the other six, all were receiving adalimumab every other week. All seven remained on their original treatment and 29% were in remission at week 56 [45]. Data from the RA population show that approximately 5% (58 of 1062) of patients in three large studies developed low-titer antibodies to adalimumab at least once during treatment, which neutralized the medication in vitro. Patients who were treated concomitantly with methotrexate experienced a lower rate of antibody development than those treated with adalimumab alone (1% versus 12%) [40].

CERTOLIZUMAB

Structure and Mechanism of Action

Certolizumab pegol, or CDP870 (UCB, Smyrna, Georgia), is a monoclonal humanized anti–TNF-α antibody Fab′ fragment linked chemically to polyethylene glycol for subcutaneous administration. The Fab′ fragment is produced by microbial (*Escherichia coli*) fermentation rather than mammalian cell culture. Certolizumab is engineered by grafting the short hypervariable complementarity-determining regions derived from the murine monoclonal antibody HTNF40 onto an otherwise nearly human Ig Fab′ fragment (IgG γλκ), maintaining the biologic potency of the original antibody. A maleimide connects the Fab′ fragment to two cross-linked chains of polyethylene glycol, each weighing 20 kd. These site-specific polyethylene glycols lengthen the antibody's half-life while maintaining binding activity [47]. Certolizumab has no fragment crystallizable (Fc) region; it does not cause antibody-dependent cell-medicated cytotoxicity, fix complement, induce apoptosis in human peripheral blood-derived monocytes or lymphocytes, or cause neutrophil degranulation. Its sole pharmacologic activity is the neutralization of both membrane and soluble TNF-α, for which it has a high affinity; it does not bind lymphotoxin (TNF-β) [48]. Efficacy in both induction and maintenance of remission in patients with CD has been demonstrated in two randomized controlled trials [47,49].

Pharmacokinetics

A single intravenous dose of certolizumab in patients with CD yields a $T_{1/2}$ of approximately 2 weeks [49]. In healthy subjects administered a single intravenous (up to 10 mg/kg) or subcutaneous (up to 800 mg) dose, a linear relationship between dose and C_{max} and area under the curve was observed. $T_{1/2}$ was approximately 14 days for all doses, and bioavailability approximates 80% after a subcutaneous administration [48]. Pharmacokinetic data were similar in RA patients given a single infusion of certolizumab at doses of 1, 5, or 20 mg/kg [50].

Immunogenicity

Antibodies to certolizumab were found at least once over 12 weeks in 12.3% of CD patients receiving three doses of subcutaneous 400 mg; 37.5% of patients in this group were on concomitant immunomodulators. Although plasma concentrations of certolizumab seemed to be lower in the antibody-positive patients, no decrease in efficacy was found at week 12 [47]. Although specific data are not available, anticertolizumab levels were low or undetectable in patients with RA given a single intravenous infusion of certolizumab (1–20 mg/kg). After a second infusion, however, antibodies were detected in all treatment groups with a lower incidence of antibodies identified in the higher-dose groups [50].

SELECTIVE ADHESION MOLECULE INHIBITORS

Natalizumab (Tysabri; Elan Pharma, Letchworth, England) and MLN02 (Millenium Pharmaceuticals/Genentech, Cambridge, Massachusetts) are antibodies that target α4 or α4β7 integrins and are members of a new class of biologic agents called selective adhesion molecule inhibitors.

α_4 Integrin: Structure and Physiology

The emigration of leukocytes from the vascular space to inflamed tissue is a complicated process involving multiple leukocyte-endothelial interactions including tethering, rolling, firm adhesion, spreading, and migration. Leukocyte adhesion to activated endothelium is mediated primarily by the α_4 integrins [51]. α_4 Integrin is part of a large family of integrins, or cell-surface adhesion molecules, which mediate both intercellular and cell to extracellular matrix interactions [52]. Integrins are transmembrane heterodimers, consisting of 1 of 18 alpha and 8 beta subunits that combine to form more than 24 different integrin receptors [53]. As reviewed by Sandborn and Yednock [54], α_4 integrin is expressed on all types of white blood cells, but at only low levels on neutrophils, and can pair with either the β_1 or β_7 subunit. Endothelial ligands recognized by α4 integrin include vascular cell adhesion molecule-1 and mucosal addressin cell adhesion molecule-1 (MadCAM-1), both of which are expressed on postcapillary venules. Vascular cell adhesion molecule-1 is induced ubiquitously at sites of inflammation, whereas MadCAM-1 is expressed constitutively on the endothelium within Peyer's patches and other gut-associated lymphoid tissues. Extracellular ligands for α4 integrin include fibronectin, osteopontin, and thrombospondin and ADAM28 (a disintegrin and metalloprotease domain 28); the interaction of these ligands with α_4 integrin imparts various effects on the inflammatory process.

NATALIZUMAB

Structure and Mechanism of Action

Natalizumab is a recombinant humanized antibody derived from a murine monoclonal antibody (AN100226m) that targets human α_4 integrin. AN100226m is a potent inhibitor of in vitro interactions between $\alpha_4\beta_1$ and vascular cell adhesion molecule-1 and has been shown to reverse experimentally induced

autoimmune encephalomyelitis, an animal model of multiple sclerosis [55]. The complementarity-determining region of the hypervariable region of the gene encoding AN100226m was grafted onto a human IgG_4 framework, such that the resulting antibody is 95% human and only 5% mouse-derived [54]. The IgG_4 isotype does not activate complement, has a low affinity for Fc receptors, and a longer $T_{1/2}$ in circulation than other subclasses of human IgG [56].

Pharmacodynamics and Efficacy in Inflammatory Bowel Disease

Improvement or resolution of colitis in the cotton-topped tamarin has been demonstrated after treatment with monoclonal antibody to α_4 integrin, either alone [57] or in combination with β_7 [58]. There are conflicting data for induction of remission in patients with CD: although an initial small trial should promise [59], two other larger randomized controlled trials including ENACT I did not show significant differences over placebo in clinical response or remission rates for primary end points [60,61]. In contrast, the Efficacy of Natalizumab in CD Response and Remission (ENCORE) study (n = 509) demonstrated a significant benefit in both clinical response and remission in patients with CD and an elevated C-reactive protein who were treated with three doses of natalizumab at 0, 4, and 8 weeks compared with placebo [62]. In those patients who were initial responders to natalizumab (n = 339), ENACT 2 demonstrated efficacy in maintenance of remission [60] and concomitant use of immunomodulators did not affect efficacy [63]. An open-label extension study of ENACT 2 showed that 84% of patients who were in remission after 1 year remained in remission for a total of 2 years after continued monthly treatment with natalizumab [64]. A small open-label pilot study in patients with UC who received one infusion of 3 mg/kg showed significant clinical improvement at week 2 as measured by the Powell-Tuck score ($P = .004$) [65].

Pharmacokinetics

In patients with CD, the mean plasma $T_{1/2}$ of natalizumab (3 mg/kg) was 4.8 days, in contrast to 8.7 days in healthy volunteers [59]. The shorter half-life in CD patients may be related to higher levels of circulating $\alpha 4^+$ cells than in healthy patients, although this has not been confirmed in other studies [66]. After a single infusion (3 mg/kg), a mean C_{max} of (52.8 μg/mL) was achieved at 1 hour, and most patients had detectable serum levels of natalizumab at 4 weeks, with a mean serum concentration of 0.99 μg/mL. In vitro studies suggest that a minimum concentration of 3 μg/mL is needed to produce appropriate saturation of at least 80% of membrane-bound α4 integrins, which may explain why 50% of patients treated at the previously stated dose required rescue therapy by week 4 [59]. A transient but significant increase in lymphocytes (both T- and B-cell subsets) from baseline occurred at postinfusion weeks 1, 2, and 4 in the natalizumab-treated group; this phenomenon has been observed in other animal and human adhesion molecule antibody studies and is postulated to occur because $\alpha 4^+$ lymphocytes are prevented from

migrating through the vascular endothelium and stay within the intravascular space [59].

Immunogenicity

In the induction study by Gordon and coworkers [59], 2 (11%) of 18 patients developed transient low-titer non–anti-idiotypic antibodies to natalizumab detectable at one out of five visits during the 12-week trial follow-up period. One of the patients became antibody positive at week 8 but remained in remission through at least week 12. The other patient never experienced remission and developed antibodies at week 4. Antibodies to natalizumab developed in 13 patients (7%) at week 12 in the induction study by Ghosh and coworkers [61]; one of these patients reported mild itching and erythema with administration of the second dose, whereas another patient with a similarly mild infusion reaction did not have antibodies to natalizumab. Similarly, 8% (53 of 650) and 9% (36 of 390) in the ENACT-1 and 2 studies, respectively, tested positive for antibodies to natalizumab ($\geq$0.5 μg/mL). In the ENACT-2 study, patients were further classified as having transient (3%) or persistent antibodies (6%), the latter defined as two positive tests at least 6 weeks apart. Concomitant immunomodulator and corticosteroid therapy seemed to protect against antibody formation, but small absolute numbers prevented statistical analysis. Acute infusion reactions were seen in 45% of antibody-positive patients compared with 9% of antibody-negative patients in ENACT-I ($P < .001$): of the five patients with a serious hypersensitivity reaction, three were antibody-positive. In ENACT-2, 19% of antibody-positive patients had either an acute infusion reaction or a hypersensitivity-like reaction as compared with 7% of antibody-negative patients ($P = .02$). There was no significant difference in response at week 12 between antibody-positive and -negative patients in the ENACT-1 study (53% versus 62%, $P = .18$). In ENACT-2, of the patients who responded to induction therapy and were randomized to maintenance therapy with natalizumab, none of seven patients with persistent antibodies maintained a response through week 60, compared with three of four patients who had transient antibodies and 56% (87 of 156 patients) who were negative for antibodies [60].

MLN02

Structure and Mechanism of Action

MLN02 is a humanized monoclonal antibody that specifically recognizes the α_4B_7 heterodimer but does not cross-react with the individual component monomers [67]. The major ligand for α_4B_7 is MadCAM1, which is selectively expressed on the endothelium of the intestinal vasculature with increased concentrations at sites of inflammation [68]. Further, MadCAM1+ venules were found to be abundant in the resected tissue of patients with both CD and UC. MadCAM1+ venules were found to a greater extent in ulcer bases ($P < .001$) and deeper layers of mucosa within the lymphoid aggregates in patients with CD compared with UC, however, and it has been postulated that MadCAM might contribute to transmural inflammation in CD [69].

Pharmacodynamics and Efficacy in Inflammatory Bowel Disease

In mild to moderate UC patients (n = 181) given MLN02, 0.5 or 2 mg/kg, or placebo on Days 1 and 29, significantly more patients receiving MLN02 at either dose compared with placebo experienced clinical remission and response, endoscopic remission and improvement [67]. In a similarly designed study in patients with mild to moderate CD (n = 185), neither the 0.5 or 2 mg/kg group achieved the primary end point of clinical response at 2 months, but clinical remission was seen in 36.9% of the 2 mg/kg group compared with 20.7% of the placebo group ($P < .05$) [70].

Pharmacokinetics

In patients with UC, the mean (± SD) C_{max} was 12.5 ± 2.5 μg/mL in the 0.5 mg/kg group and 52 ± 10.4 μg/mL in the 2 mg/kg group, with $T_{1/2}$ of 9 and 12 days, respectively. $\alpha_4\beta_7$ saturation of $CD4^+CD45RO^+$ T cells in the peripheral circulation was greater than 90% in both groups at weeks 4 and 6 [67].

Immunogenicity

In a study evaluating MLN02 for active UC, 44% of patients developed antibodies to MLN02 by week 8, with 24% having titers ≥1:125 (38% and 11% of patients in the 0.5 and 2 mg/kg groups, respectively). A similar rate of clinical remission was seen in patients with titers ≥1:125 compared with placebo (12% versus 14%). In patients treated with MLN02 with absent or lower antibody titers, however, the clinical remission rate was 42% (*P* value not given). Additionally, in patients with ≥1:125 antibody titer, α_4B_7 binding sites on the $CD4^+CD45RO^+$ T lymphocytes became unsaturated (numerical results not provided), whereas in antibody-negative patients or those with a lower titer, α_4B_7 binding sites remained saturated. Only one clinically relevant infusion reaction (hives and mild angioedema) was noted in a patient treated with MLN02 who had an antibody titer of 1:3125. Overall, higher antibody titers were associated with lower doses and seemed to result in both lower rates of α_4B_7 saturation and remission. Although using higher doses of MLN02 may decrease antibody formation, no additional clinical or endoscopic benefits were observed [67]. Future studies may consider the concomitant use of immunomodulator therapy, pretreatment with corticosteroids, and regular infusions of medication, all of which have been shown to decrease antibody formation with infliximab.

VISILIZUMAB

Structure and Mechanism of Action

Visilizumab (Nuvion; PDL BioPharma Inc., Fremont, California) is a humanized IgG_2 monoclonal antibody (HuM291) that binds the CD3ϵ chain of the T-cell receptor expressed on activated T cells. Visilizumab was designed to capitalize on the potent immunosuppressive effect of OKT3 (a mouse monoclonal antibody specific for the human CD3 complex on T cells, used primarily to help prevent acute allograft rejections), while simultaneously minimizing both the neutralizing antimouse antibody response and the adverse effects of the

cytokine-release syndrome resulting from OKT3-mediated T-cell activation induced by cross-linking of T cells and Fcγ receptor-bearing cells [71]. Visilizumab has a mutated Fc domain (non-FcR type II-binding) that causes less T-cell activation and less cytokine release: with only 10% mouse amino acid, it is also less immunogenic [71]. The IgG_2 isotype confers the longest in vivo half-life among all human IgGs, and decreases complement activation and interaction with type I and III FcRs [72]. Visilizumab may induce activated T-cell apoptosis, probably secondary to sustained surface T-cell receptor signaling [73]. Further, visilizumab may induce production of interleukin-10, a potent anti-inflammatory cytokine released mainly from regulatory T-cells which inhibits Th1 T-cell cytokine release and down-regulates antigen-presenting cells [74].

Pharmacodynamics

Visilizumab has been studied in an open-label phase I trial in steroid-refractory active UC, with patients receiving intravenous 10 μg/kg/d (n = 24) or 15 μg/kg/d (n= 8) for 2 consecutive days; response and remission rates at day 30 were 79% and 54%, respectively, for the 10 μg/kg group and 100% for both response and remission in the 15 μg/kg group [74,75]. Sixty-three percent of patients receiving visilizumab had symptoms consistent with cytokine-release syndrome, including nausea, chills, fever, headache, and arthralgias, occurring 1 to 3 hours postinfusion. A transient T-cell depletion lasting for a mean of 3 weeks postinfusion was also noted. Recent data from an open-label trial in infliximab-refractory CD patients given two consecutive doses of visilizumab demonstrated response in 6 of 8 patients and one remission at 2 months posttreatment [76].

In a small phase 1 study of visilizumab in patients with glucocorticoid refractory acute graft-versus-host disease, T lymphocytes were reduced from a median baseline of 65/μL to 6/μL after infusion; T cells remained 1 to 2 logs below preinfusion level for at least 14 to 28 days postinfusion. There was a direct relationship between the time at which visilizumab levels dropped below 100 ng/mL and peripheral T-cell count recovery to >100 cells/μL. Further, special staining of T cells in one patient showed that small numbers of residual circulating T cells were coated with visilizumab in vivo for up to 21 days and that these cells had a reduced number of free CD3 sites [72].

Pharmacokinetics

In the same study, six patients received visilizumab, 0.25 mg/m^2 or 1 mg/m^2 every other day for 2 weeks. Mean $T_{1/2}$ were 103 and 177 hours in the 0.25 and 1 mg/m^2 groups, respectively. In the three patients treated at 1 mg/m^2, trough drug levels increased proportionately with repeated dosing suggesting that visilizumab saturates drug receptors, leading to concern for drug accumulation, delayed clearance, and potential increased toxicity. Subsequent patients enrolled in this study received a single dose of 3 mg/m^2, resulting in a C_{max} of 2217 ± 148 ng/mL, $T_{1/2}$ 162 hours, and a mean systemic serum clearance 6.99 ± 1.23 L/m^2/h [72].

Immunogenicity

No human antibodies against visilizumab were detected in any of the 13 graft-versus-host disease patients who survived until day 42 after infusion; additionally, no patients suffered any allergic reactions. T-cell depleted transplants and in vivo T-cell depleting therapies are associated with a risk of developing Epstein-Barr virus posttransplant lymphoproliferative disease. In the first open-label trial in UC patients as described previously, no patients with baseline positive Epstein-Barr virus titers were studied, but there is a larger ongoing open label trial underway that is permitting Epstein-Barr virus–positive patients to enroll [72].

SUMMARY

The pharmacology of each biologic agent is important regarding the dose required to achieve benefits, duration of therapeutic effect, and the induction of immunogenicity. Comprehension of the individual pharmacology, pharmacodynamics, and pharmacokinetics, in addition to the impact of concomitant immunomodulation on immunogenicity allows optimization of each biologic agent in the appropriate inductive or maintenance setting of IBD.

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Infliximab Use in Luminal Crohn's Disease

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Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract with a relapsing and remitting course that affects more than 400,000 people in the United States [1]. Classic symptoms of CD include abdominal pain, diarrhea, and weight loss, with extraintestinal manifestations such as arthritis, erythema nodosum, pyoderma gangrenosum, conjunctivitis, uveitis, and renal stones [2]. Because of the chronic nature of the disease and the significant morbidity and health care costs accrued by those afflicted, much attention has been devoted to CD. Significant advances in understanding its origin and pathogenesis have been made recently, most based on sophisticated animal models and a deepening understanding of immunologic events [3]. Despite this progress, standard medical treatments have not provided the desired level of short- and long-term disease control: approximately 70% of patients require surgery at some point [4].

The primary goals of pharmacologic intervention in CD are to improve the patient's quality of life, reduce the risk of CD-related complications, and avoid surgical intervention [5]. In the early years, sulfasalazine and steroids were the mainstays of treatment. More recently, antimetabolites such as azathioprine and methotrexate have been used successfully in both the induction and maintenance of remission, but they have a slow onset of action and risk for serious toxicity, and remission rates can be as low as 40% [6]. In 1998, the emergence of infliximab, a biologic agent active against tumor necrosis factor alpha (TNF-α), represented an important advance in the treatment of CD.

The Food and Drug Administration (FDA) approved infliximab in May 1998 for two indications in CD: (1) as single-dose therapy for the treatment of patients who have moderate-to-severe inflammatory CD and (2) as a three-dose regimen

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for the treatment of fistulous CD [7]. Since its introduction, infliximab has gained labeling for maintenance therapy in both luminal and fistulizing disease. It has approval for other conditions and has been used successfully for extraintestinal manifestations of CD.

This article discusses the efficacy and safety of infliximab in luminal CD. To date, nearly 800,000 patients have been treated with infliximab worldwide (R. Diamond, personal communication, 2005). Infliximab has proven to be safe and effective for patients affected with CD. This article offers the background and clinical data on its use.

BACKGROUND

TNF is a proinflammatory cytokine that plays a pivotal role in the pathogenesis of CD [8,9]. Direct evidence from both human and animal studies supports the clinical importance of TNF in the initiation and promotion of intestinal inflammation. Mucosal biopsy specimens from the lamina propria of patients who have CD have been shown to express high levels of TNF [10]. Increased TNF-α levels also have been found in the serum, urine, and stool, with the magnitude of elevation paralleling disease activity [10–12].

TNF is a 157-amino acid protein produced and secreted by T lymphocytes, monocytes, and macrophages. TNF is produced as a 26-kd transmembrane precursor, which is cleaved to the secreted 17-kd soluble form by the metalloproteinase desintegrin (TNF-α converting enzyme) [13,14]. This 17-kd monomer then aggregates to form the biologically active 51-kd trimeric complex that binds to either the 55-kd (known as p55 or TNF-α R1) or the 75-kd (known as p75 or TNF-α R2) receptors on various cells [15,16]. The binding of TNF to its receptor leads to numerous intracellular signaling events by the nuclear factor kB and Jun kinase pathways through the activation of phosphatidylcholine-specific phospholipase C, sphingomyelinases, G proteins, and protein kinase A and C [17–19]. Activation of these pathways allows the transcription of numerous genes involved in the inflammatory process.

With increasing knowledge about the central role of TNF in the inflammatory cascade, considerable research has been devoted toward developing novel biologic agents to neutralize the activity of these proinflammatory cytokines. Recombinant technology has allowed the development of monoclonal antibodies that target individual cytokines, thus reducing the inflammatory process. TNF-neutralizing antibodies have proven to be effective in various animal and human studies; three therapeutic agents, infliximab (a chimeric monoclonal anti–TNF-α antibody), etanercept (a recombinant human TNF receptor fusion protein), and adalimumab (a human monoclonal antibody), have been approved for clinical use. All three agents have been highly effective in rheumatoid arthritis (RA), but only infliximab has FDA approval for CD [20,21].

Infliximab is a chimeric monoclonal IgG1 antibody (75% human, 25% mouse) [22,23]. Infliximab binds to the soluble bioactive TNF and membrane-bound TNF, neutralizing its biologic activity. Binding to membrane-bound TNF leads to antibody-dependent cellular toxicity or

complement-dependent cytotoxicity of cells expressing TNF on their surface [24]. Additionally, it has been shown that infliximab induces apoptosis of activated T lymphocytes by activation of caspase 3, in a Fas-independent manner [25]. Through the decreased expression of T cells, especially the T-helper 1 subclass, there is also decreased expression of other proinflammatory cytokines, including interferon gamma and interleukin 2, further reducing the inflammatory cascade [26].

INDUCTION OF REMISSION

Derkx and colleagues [27] authored a case report of a 12-year-old girl who had refractory CD who achieved complete but temporary remission after treatment with infliximab. This case report led to two initial open-label trials [28,29] followed by a third placebo-controlled trial [21] evaluating the induction of remission in patients who had active CD that was unresponsive to conventional corticosteroid therapy.

The pilot study was an open-label clinical trial conducted by van Dullemen and colleagues [28] in which eight patients were given a single intravenous infusion of 10 mg/kg of body weight and two patients were given a single intravenous infusion of 20 mg/kg of body weight. The study period was 8 weeks. Patients were evaluated by both the Crohn's Disease Activity Index (CDAI) at weeks 0, 2, 4, 6, and the CDAI of Severity at weeks 4 and 8. One patient was excluded from the analysis because of incomplete data (colonic perforation on entry from colonoscopy). Entry requirements specified failure to achieve remission with a 20-mg/d or higher dose of prednisone. The mean CDAI score at baseline was 257 (range, 202–355), and all patients at baseline had endoscopic evidence of active inflammation of the colon or terminal ileum. Of the nine evaluable patients, eight reported improvement in subjective symptoms within 1 week after infusion. These eight were in remission (CDAI score <150) by week 2, with a mean CDAI score of 114. At week 4, repeat videoendoscopy revealed near total endoscopic resolution of active inflammation. By week 8, the mean CDAI score decreased to 69, and seven of nine evaluable patients (78%) were in clinical remission. Also noted, the extraintestinal manifestations of CD (pyoderma gangrenosum, arthralgias/arthritis) improved substantially after treatment, and C-reactive protein levels decreased in all nine patients, reaching normal levels within 2 weeks. The average duration of response was 4 months.

McCabe and colleagues [29] conducted an open-label, multicenter, dose-escalating study. Twenty steroid-refractory patients were randomly assigned to receive single intravenous infusions of 5, 10, or 20 mg/kg of body weight. The study period was 12 weeks. CDAI scores at week 0 ranged from 220 to 400, and all patients had been receiving corticosteroid therapy for at least 1 month before entry. Patients were evaluated by the CDAI at weeks 0, 2, 4, 8, and 12 and by endoscopy at weeks 0, 4, and 8. Clinical response was defined as a reduction in CDAI score of at least 70 points from baseline, and remission was defined as a CDAI score below 150. In patients receiving 10 mg/kg of body

weight, clinical response and remission were achieved in one of five (20%) and zero of five (0%), respectively, with little improvement in their week 8 endoscopic scores. Clinical responses for those receiving between 5 and 20 mg/kg of body weight were between 50% and 80% at week 12, and among those achieving remission were between 25% and 60% at week 12. Endoscopic scores likewise improved for those receiving between 5 and 20 mg/kg of body weight. The highest response and remission rates were noted with the 10 mg/kg of body weight dose (80% and 60%, respectively), although this result was not statistically significant. These findings led the authors to conclude that infliximab is safe and effective in patients who have active, steroid-unresponsive CD.

Targan and colleagues [21] conducted the first multicenter, double-blind, placebo-controlled, randomized trial of infliximab. One hundred eight patients who had moderate-to-severe CD resistant to treatment were enrolled in the study. The length of the initial study was 12 weeks with the primary end point defined as a reduction of 70 points or more in the CDAI score at the week 4 evaluation that was not accompanied by a change in any concomitant medication. All participants in the study had had CD for at least 6 months, had CDAI scores ranging between 220 and 400, and had been taking prednisone up to a maximum of 40 mg/d for 8 weeks or more before entry. Twenty-five patients were randomly assigned to receive placebo (serum human albumin), and 83 patients were randomly assigned to receive infliximab at doses of 5, 10, or 20 mg/kg of body weight. As in the previous two studies, the response to the medication was rapid, with 61% of infliximab recipients having a clinical response by week 2 after infusion, as compared with 17% in the placebo group ($P < .001$). Similarly, 27% of infliximab recipients were in remission (CDAI score <150) by week 2, compared with 4% in the placebo group ($P = .06$). Sixty-five percent of the infliximab recipients met the primary end point of a reduction of 70 or more points in the CDAI score at week 4, compared with 17% of those given placebo ($P < .001$). The difference in the rates of clinical response between the infliximab-treated groups and the placebo group remained significant through 12 weeks of follow-up, with an overall rate or response of 41% in the infliximab-treated groups as compared with 12% in the placebo group ($P = .008$). The difference in the percentage of patients in remission was not significant at 12 weeks, however; the overall rate of remission in the treated group was 24%, as compared with 8% in those receiving placebo ($P = .31$). There was no statistically significant difference between the three doses of infliximab used in the trial, although the 5-mg/kg of body weight dose consistently yielded the highest response and remission rates.

An open-label extension of the study also was conducted to examine the clinical response of re-treating those individuals who failed to meet the primary end point (clinical response as defined as a decrease of CDAI score by more than 70 points at week 4 after initial infusion). Nineteen patients who had initially received placebo and 29 patients who had received infliximab were given open-label infliximab at a dose of 10 mg/kg of body weight at week 4. The initial placebo group responded similarly to those who were treated with

infliximab in the blinded phase of the study, with 58% having a clinical response and 47% achieving remission by week 4 after the open-label infusion. The patients initially treated with infliximab were less responsive to the open-label treatment (their second infusion), with 54% having a clinical response and 17% achieving remission by week 4 after the open-label infusion. This finding initially raised some concern that response to repeated infusions would not be consistent [30].

MAINTENANCE OF REMISSION

Further studies were needed to evaluate the safety and efficacy of repeated infusions of infliximab for the maintenance of remission in patients who had CD. Rutgeerts and colleagues [31] conducted a follow-up study of repeated infusions of infliximab in patients who had a clinical response at week 4 in the study conducted by Targan and colleagues [21]. Seventy-three patients were enrolled to receive either infliximab (10 mg/kg of body weight) or a placebo (serum human albumin) every 8 weeks through week 36 with follow-up through week 44. The primary end points of the study were clinical response and remission based on the CDAI score as defined in the previous Targan study [21].

The median time to loss of clinical response was greater in the re-treatment arm: more than 47 weeks with active drug, versus 37 weeks in the placebo arm ($P = .057$). Most importantly, proportions of remission were higher in the re-treatment arm at the end of the trial (44 weeks) than at the beginning of the trial (12 weeks). Clinical response was not as strongly maintained. Specifically, clinical remission increased from 37.8% at week 12 to 52.9% at week 44 in the re-treatment arm. In the placebo arm, clinical remission decreased from 44.4% at week 12 after infliximab to 20% at week 44. Thus, an individual patient in the study who received a single dose of infliximab had a 20% chance of maintaining remission by week 44. The differences between the re-treatment arm and the placebo arm at week 44 were statistically significant for remission ($P = .013$) and trended toward statistical significance for clinical response ($P = .16$).

The ACCENT I trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long term Treatment Regimen), at the time the largest clinical trial in patients who had symptomatic CD, was conducted to assess the benefit of maintenance infliximab therapy in patients who responded to a single dose of infliximab [32]. Five hundred seventy-three patients who had a CDAI score of at least 220 received a 5-mg/kg intravenous infusion of infliximab at week 0. Patients then were randomly assigned to one of three groups. Group I received infusions of placebo at weeks 2 and 6 and then every 8 weeks until week 46. Group II received repeat infusions of 5 mg/kg of infliximab at weeks 2 and 6 and then every 8 weeks until week 46. Group III received 5 mg/kg of infliximab at weeks 2 and 6 followed by 10 mg/kg every 8 weeks until week 46. Primary end points of the study were the proportion of patients who responded at week 2 and were in remission (CDAI score <150) at week 30 and the time to loss of response up to week 54 in patients who responded. Three hundred thirty-five patients (58%) responded to a single infusion of infliximab within 2 weeks. At

week 30, 23 of 110 group I patients (21%) were in remission, compared with 44 of 113 of group II patients (39%) ($P = .003$) and 50 of 112 group III patients (45%) ($P = .0002$). Throughout the 54-week trial, the median time to loss of response was 38 weeks for group II and more than 54 weeks for group III, compared with 19 weeks for group I. The results of this landmark study showed that patients who have CD and who respond to an initial dose of infliximab are more likely to maintain remission when treated with infliximab therapy every 8 weeks.

FISTULIZING DISEASE

Present and colleagues [33] conducted a randomized, double-blind, placebo-controlled trial that demonstrated the efficacy of infliximab in treatment of fistulizing CD. Ninety-four patients who had actively draining abdominal or perianal fistulas were randomly assigned to receive either infliximab at 5 mg/kg, infliximab at 10 mg/kg, or placebo at 0, 2, and 6 weeks. The primary end point of the study was defined as a 50% reduction in the number of draining fistulas present at baseline, which was maintained for at least 4 weeks. Sixty-eight percent of the patients who received 5 mg/kg of infliximab and 56% of those who received 10 mg/kg achieved the primary end point, as compared with 26% of the patients in the placebo group ($P = .002$ and $P = .02$, respectively). Additionally, 55% of patients receiving 5 mg/kg of infliximab and 38% of patients receiving 10 mg/kg of infliximab had complete closure of all fistulas, as compared with 13% of patients treated with placebo ($P = .001$ and $P = .04$, respectively). The median duration of fistula closure was 3 months.

A second trial by Sands and colleagues [34] confirmed the efficacy of infliximab in both induction and maintenance treatment of fistulizing CD. Three hundred six patients who had actively draining fistulas received three doses of infliximab (5 mg/kg) at 0, 2, and 6 weeks. At week 14, patients who responded to therapy (defined as closure of at least 50% of fistulas present at baseline maintained for at least 4 weeks) were randomly assigned into two groups: group I received maintenance doses of placebo every 8 weeks beginning at week 14; group II received maintenance doses of infliximab (5 mg/kg) every 8 weeks beginning at week 14. Patients were monitored for 54 weeks. One hundred ninety-five of 306 patients (69%) had a fistula response at week 14. The median time to loss of response through week 54 was 14 weeks for placebo-treated patients and more than 40 weeks for patients treated with infliximab (5 mg/kg) ($P < .001$).

The efficacy of infliximab as maintenance therapy for sustaining fistula closure was evaluated in the ACCENT II trial [35]. Patients received infliximab (5 mg/kg) at 0, 2, and 6 weeks. Of the 282 patients who completed the study through week 14, 195 patients (69%) achieved closure of at least 50% of their draining fistulas sustained over 1 month. These patients then were randomly assigned to receive either infliximab (5 mg/kg) (n = 96) or placebo (n = 99) every 8 weeks through week 46. By week 30, 48% of the infliximab-treated patients maintained fistula response, compared with 27% of patients receiving placebo. At week 54, 36% of the infliximab-treated patients maintained fistula

remission compared with 19% of the placebo group. The median time to loss of response was more than 40 weeks in the infliximab-treated group compared with 14 weeks in the placebo group. Further analysis of the data from this study has revealed that the efficacy of infliximab was independent of the baseline number of draining fistulas [35]. Another important finding of this study was that fistula-related abscesses were uncommon despite concern that these might occur as a result of the recurrence of inflammation beneath the superficially healed fistula tract [35]. (A more detailed description of infliximab use in fistulizing CD is found elsewhere in this issue.)

SAFETY

Although infliximab has revolutionized the management of CD, there have been serious side effects reported with its use. These side effects include acute infusion reactions, serum-sickness reactions, infections including sepsis and reactivation of tuberculosis, autoantibody formation, hepatotoxicity, demyelinating reaction, and lupuslike reactions. To date, infliximab has proven generally safe and tolerable, but clinicians need to be aware of such events, and patients should be counseled about these toxicities before initiating therapy.

Acute infusion reactions are defined as any adverse event occurring during or within 2 hours of an infusion. In the combined safety data from all clinical trials, approximately 20% of infliximab-treated patients experienced an infusion reaction, compared with approximately 10% of patients receiving placebo [36]. Most reactions were mild and nonspecific with symptoms including headache, nausea, fever, chills, pruritus, urticaria, chest tightness, and dyspnea. Serious infusion reactions occurred in less than 1% of patients and included anaphylaxis or anaphylactic-like reactions with clinical symptoms including hypotension, laryngeal/pharyngeal edema, severe bronchospasm, and seizure [36]. Approximately 3% of patients had infusion reactions that led to discontinuation of infliximab; and all patients recovered with treatment or discontinuation of the infusion [36]. Strategies to decrease the incidence of infusion reactions include premedication with acetaminophen, intravenous diphenhydramine, and famotidine approximately 30 minutes before infusion [6]. It also has been demonstrated that infusion reactions are more common in those individuals who develop antibodies to infliximab (ATIs). The approach to reducing the frequency of ATIs and infusion reactions is discussed later.

Treatment with infliximab also has been associated with delayed hypersensitivity or serum sickness–like reactions. These reactions can occur up to 14 days after an infusion; symptoms include headache, fever, rash, sore throat, myalgias, polyarthralgias, hand and facial edema, and dysphagia. At the Mayo Clinic 14 of 500 patients (2.8%) experienced serum sickness–like reactions with most (11 of 15) occurring after the second infusion; the median time from the last infusion was 10.5 months [37]. In the ACCENT I trial, in which patients received scheduled infusions every 8 weeks, the frequency of delayed hypersensitivity reaction was 2% [32]. The incidence of these reactions is associated with the formation of ATIs and a prolonged interval between infusions.

Serious infections (ie, infections requiring treatment with parenteral antibiotics or hospital admission) have been documented in patients receiving infliximab therapy. In clinical trials, infections requiring treatment were reported in 36% of infliximab-treated patients, compared with 26% of those receiving placebo [36]. The infections most commonly reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Serious and even fatal infections reported include sepsis, abscess, pneumonia, cellulitis, tuberculosis, disseminated coccidiomycosis, histoplasmosis, listeriosis, aspergillosis, *Pneumocystis carinii*, cytomegalovirus, and systemic candidiasis [36]. In clinical trials, the frequency of infections was similar in patients receiving TNF-antagonist therapy and placebo [36]. Mayo Clinic reported 41 of 500 patients (8.2%) developed an infection while receiving infliximab therapy [37]. Twenty patients had a serious infection: two cases of lethal sepsis; eight pneumonias, of which two were fatal; six viral infections, including three varicella-zoster virus infections; two abdominal abscesses requiring surgery; one case of arm cellulitis; and one case of histoplasmosis. Of note, most infections occurred after three or fewer infusions, and the rate of infectious events did not correlate with the number of infusions. Infliximab should not be given to patients who have active infection until the infection has been properly treated and cleared. Clinicians should be cautious when using infliximab in patients who have a history of chronic or recurrent infection. If a patient develops a serious infection while receiving therapy, infliximab should be discontinued.

TNF-α plays a central role in the host immune response to *Mycobacterium tuberculosis* infection. The release of TNF-α in response to a mycobacterial infection increases the ability of macrophages to phagocytose and kill mycobacteria [38,39]. TNF-α production also is a requirement for the formation of granulomas, which sequester mycobacteria and prevent their dissemination, maintaining tuberculosis in the latent phase [40,41]. Not surprisingly, with the inhibition of the biologic activity of TNF, a number of infectious adverse events have been observed. In May 2001, Keane and colleagues [42] identified 70 cases of tuberculosis in individuals receiving treatment with infliximab for CD or RA. The denominator of patients exposed to the drug at that time was 147,000. Sixty-four of the 70 cases were from countries of low incidence, and the median interval from the start of treatment until the development of disease was 12 weeks. Of note, 40 patients had extrapulmonary disease, including 17 cases of disseminated disease. The close temporal association of the initiation of treatment and the development of tuberculosis suggests activation of latent disease rather than new infection.

Screening for latent tuberculosis infection is advised in all patients before treatment with infliximab [43]. Screening should include a careful history (looking for exposure to *M tuberculosis*), a tuberculin skin test (TST), and a chest radiograph. The American Thoracic Society and Centers for Disease Control recommend screening patients who are being considered for TNF-blocker treatment for latent tuberculosis infection with purified protein derivative [36,44]. Individuals who have a positive TST must be thoroughly assessed for active tuberculosis. In the

setting of active disease, patients must be treated with a full course of therapy before initiation of treatment with an anti-TNF agent. Once active disease has been excluded, TST-positive individuals should be considered candidates for treatment of latent infection. The recommended treatment regimen is isoniazid, 300 mg/d, for 9 months [45]. A dilemma arises concerning treatment of individuals who received childhood bacille Calmette-Guérin (BCG) vaccination and have a positive TST. A conservative approach may be appropriate, disregarding BCG vaccination as the cause of the positive skin test, and initiating prophylactic treatment before starting infliximab therapy [46].

TST cut-off criteria for patients receiving TNF-blocker therapy have been suggested [46]. For example, TST-negative patients who have no epidemiologic risk factors for *M tuberculosis* infection (induration <10 mm) can receive TNF-blocker therapy without additional investigation or therapy [46]. TST-positive patients (induration ≥10 mm, or ≥5 mm in those who have coexisting epidemiologic risk factors) require further investigation to rule out active disease [46]. Clinicians also should be alert to the possibility of false-negative TST reactions. A chest radiograph should be performed if warranted by the patient's medical history and epidemiologic risk factors (ie, recent exposure to the infection or travel to a high-risk area), despite a negative TST [47]. The potential for false-negative screening tests and the possibility of acquiring primary TB while receiving therapy should be discussed with patients and underscore the need for continuous vigilance on the part of clinicians for the possibility of TB in patients treated with these agents. Patients should be advised to seek medical attention if night sweats, weight loss or respiratory symptoms develop while taking these agents.

Inflammatory bowel disease often occurs when women are at reproductive age, making the impact of disease and therapy on pregnancy an important clinical issue [48]. Infliximab is currently a pregnancy category class B drug. Animal reproductive studies have not been conducted with the drug, because infliximab does not crossreact with TNF-α in species other than humans and chimpanzees [36]. No evidence of maternal toxicity, embryotoxicity or teratogenecity was observed in developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α [36]. Data from the infliximab postmarketing safety database suggest that pregnant women who have RA or CD and are exposed to infliximab before or during the first trimester of pregnancy have outcomes consistent with those expected in healthy women [36]. Katz and colleagues [49] queried the infliximab safety database maintained by the manufacture (Centocor, Inc., Malvern, Pennsylvania) for pregnancy outcomes in 133 women who had direct exposure to infliximab and in 14 who had indirect exposure through male partners. Fifty-six percent of women (74/133) were exposed to infliximab within 3 months before conception, and 45% of these (33/74) received infliximab infusions both before conception and during the first trimester. Among 65 infliximab patients with pregnancy outcome data, live births occurred in 65% (42/65), miscarriage in 17% (11/65), and therapeutic termination in 22%

(14/67). These results do not differ from those expected for the general pregnant United States population or pregnant patients who have CD and were not exposed to infliximab. Of 14 pregnancies in which there was an indirect exposure to infliximab, there were 7 live births, 1 miscarriage, 3 ongoing pregnancies, and 3 unknown outcomes. These results also suggest that inadvertent exposure to infliximab during pregnancy is safe and does not cause harm to the fetus. With such limited data, it is not known whether infliximab can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity; it is recommended that infliximab be given to a pregnant woman only if clearly needed [36].

It is not known whether infliximab is excreted in human milk or absorbed systematically after oral administration [36]. Because there is a potential risk for adverse reactions in nursing infants, patients should make a decision either to discontinue breast-feeding or to discontinue infliximab therapy before breast-feeding [50].

TNF antagonists were once considered a possible treatment for congestive heart failure. Levine and colleagues [51] demonstrated increased serum levels of TNF in patients who had advanced heart failure, and it later was shown that TNF levels correlated with the severity of heart failure [52]. Large-scale trials with TNF antagonists for the treatment of heart failure were stopped early, however, because they failed to demonstrate an improvement in clinical heart failure or mortality [53]. A phase II study (ATTACH trial) comparing infliximab with placebo in 150 patients who had New York Heart Association class III to IV congestive heart failure showed excess mortality (7 deaths versus 0 deaths) and hospitalization caused by worsening heart failure in the infliximab group [54]. Kwon and colleagues [55] reviewed postmarketing reports (to February 2002) and identified 47 patients who had congestive heart failure who had received TNF-antagonist therapy (29 etanercept and 18 infliximab). Thirty-eight (81%) developed new-onset heart failure, and nine (19%) experienced heart failure exacerbation. Of the 38 patients who developed new-onset heart failure, half had no identifiable risk factors for development of congestive heart failure, and 10 were younger than 50 years of age. After TNF-antagonist therapy was discontinued and heart failure therapy was started in these 10 patients, 3 had complete resolution of heart failure, 6 improved, and 1 died. Because these clinical implications, clinicians should be aware of the possibility of new-onset or worsening congestive heart failure in patients receiving TNF-antagonist therapy. Infliximab currently is contraindicated in patients who have moderate-to-severe congestive heart failure (New York Heart Association class III to IV) [36].

Severe hepatotoxicity, including acute liver failure requiring liver transplantation, jaundice, hepatitis, and cholestasis has been reported rarely in postmarketing data in patients receiving infliximab (letter to physicians, Centocor, Malvern, Pennsylvania, December 22, 2004). Patients who have symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice or marked liver enzyme elevations (eg, $\geq$ five times the upper limit of normal) develop, infliximab should be discontinued, and a thorough

investigation should be undertaken. Mild-to-moderate elevations of alanine aminotransferase and aspartate transaminase (alanine aminotransferase more commonly than aspartate transaminase) have been observed in patients receiving infliximab without progression to severe hepatic injury. In general, these patients were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab or modification of concomitant medications. Reactivation of hepatitis B also has occurred in patients receiving treatment with infliximab who are chronic carriers of the virus (letter to physicians, Centocor, Malvern, Pennsylvania, December 22, 2004). Chronic carriers of hepatitis B should be appropriately evaluated and monitored before the initiation of and during treatment with infliximab.

A more detailed description of safety is found elsewhere in this issue.

SPECIAL CONSIDERATIONS

Treatment with infliximab has been associated with the development of ATIs, human antibodies against the murine portion of the infliximab molecule. In the published clinical trials, 17% to 21% of patients treated with infliximab [21,32,35] and up to 60% of patients in open-label series develop ATIs [56]. ATIs are associated with an increased risk of infusion reactions and decreased response to treatment [56].

Because of the clinical implications of antibody formation, several strategies have been implemented to improve clinical response and prevent infusion reactions. Various strategies include (1) premedication with corticosteroids, (2) concomitant antimetabolite therapy, and (3) regular rather than episodic infusions [56–58]. It has been shown that the use of concomitant immunosuppressive therapy decreases the incidence of ATI formation. In the ACCENT I trial, only 4 of 64 patients receiving corticosteroids plus immunomodulator therapy (6%) developed ATIs [32]. Seventeen percent of patients receiving steroids alone and 10% of patients receiving immunomodulator therapy alone formed ATIs. In comparison, 18% of patients receiving no additional immunomodulator therapy formed ATIs. Farrell and colleagues [57] also conducted a 16-week trial in which 80 patients who had refractory CD were randomly assigned to receive 200 mg hydrocortisone or placebo immediately before receiving their first infliximab 5-mg/kg infusion. Administering intravenous hydrocortisone before medication significantly reduced ATI levels but did not eliminate ATI formation or infusion reactions [57,58].

It also has been reported that patients who receive scheduled maintenance therapy have a lower incidence of ATI formation than patients who receive infliximab on an episodic basis (as needed when they become symptomatic). In the ACCENT I and ACCENT II trials, of those patients who received scheduled infliximab infusions every 8 weeks, 8% and 13%, respectively, developed ATIs during the 1-year study period [32,35]. In the ACCENT I trial, episodic administration of infliximab resulted in ATIs in 21% of patients [32]. Likewise, in the ACCENT II trial, episodic treatment resulted in ATI formation in 21% of patients [35]. Similarly, Baert and colleagues [56] conducted a prospective

study of 125 patients who had refractory luminal or fistulizing CD who were treated episodically with infliximab. Patients who had luminal disease received a single 5-mg/kg infusion, whereas patients who had fistulizing disease received three infusions of 5 mg/kg at 0, 2, and 6 weeks. Responders were re-treated upon relapse as symptoms recurred. Sixty-one percent of patients developed ATIs. Of these patients, only 37% had clinically significant levels of antibodies to infliximab (>8 g/mL). Patients who had high ATI levels were found to have a substantially shorter duration of response (35 days) than the patients who did not form antibodies (71 days). In the ATI-positive group there also was a higher risk of infusion reactions (relative risk, 2.4). Of note, patients receiving concomitant immunomodulator therapy had less antibody formation, higher concentrations of infliximab, reduced incidence of infusion reactions, and increased duration of response. Based on the results of these studies, it now is recommended that infliximab be administered on a regular maintenance schedule and that strong consideration be given to the administration of concomitant immunomodulator therapy [56,58]. (A detailed discussion on the management of infusion reactions is found elsewhere in this issue.)

An important concern with TNF-antagonist therapy is the possible development of malignancy. In the controlled portions of clinical trials of all the TNF-α blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker than among control patients [59]. This finding is not surprising, given that many patients receiving infliximab have long histories of immunosuppressive therapies and that CD is associated with a higher risk of developing lymphomas independent of use of immunosuppressive therapy [59,60]. The finding is confounded by the increased rate of lymphoma seen in patients who have severe or long-standing RA [61]. Postmarketing surveillance of 554,000 patient-years identified 95 cases of lymphoma in patients exposed to infliximab (of which 73% were in patients who had RA and 21% in patients who had CD) [59]. This incidence of about two to three cases per 10,000 patient-years of exposure approximates the estimated rate in the normal population of 0.03 per 100 patient-years [62]. Mayo Clinic also reported that 3 of 500 patients treated with infliximab developed a malignancy (two lung cancers and one non-Hodgkins lymphoma) in which a relationship with infliximab could not be excluded [37]. The 1.5% extracolonic cancer rate possibly related to infliximab observed in the Mayo study also was similar to the rate of 18 of 1678 (1.1%) of new or recurrent cancers observed in patients who have completed clinical trials with infliximab [36], including the 1.0% rate observed in the ACCENT I trial [32]. These findings led these and other authors to conclude that a causal association between infliximab and risk of malignant disease is unlikely [63].

The occurrence of drug-induced systemic lupus erythematosus has been documented in a handful of patients treated with infliximab [64–66]. In clinical trials the induction of antinuclear and anti-DNA antibodies has been observed in 44% and 22% of patients, respectively [36]. In the ACCENT I maintenance trial, although 34% of patients assigned maintenance treatment developed

anti–double-stranded DNA, only two patients developed drug-induced lupus [32]. Mayo Clinic also reported the development of drug-induced lupus in three patients [37]. Fortunately, most of these patients do not experience sequelae or major organ involvement, and the syndrome has been promptly reversible with discontinuation of treatment.

Infliximab and other TNF blockers have been associated with rare cases of new-onset or exacerbated central nervous system demyelinating disorders. Limited data have been presented linking anti-TNF therapy in patients who have CD with new-onset multiple sclerosis–like symptoms. Mohan and colleagues [67] described 20 patients who had demyelinating process during the use of anti-TNF therapy (2 treated with infliximab and 18 treated with etanercept). Signs and symptoms from these processes included vision changes caused by optic neuritis, paresthesias, gait changes, confusion, apraxia, ascending paralysis, and facial paralysis. The most common symptom was paresthesia, which occurred in 65% of cases. The mean time to symptom onset from initiation of therapy was 5 months. In most cases, patients experienced partial or complete resolution of their symptoms following discontinuation of therapy.

COST

CD typically presents at a young age, and patients afflicted with the disease often undergo decades of health care resource use, with the potential for significant health-care costs. The estimated directed total annual medical cost of CD in 1996 dollars exceeds $1.7 billion [68], with surgery and hospitalizations accounting for 80% of the total [68]. Given the high cost of surgery and hospitalizations, newer therapies such as infliximab may reduce the overall cost of managing CD.

The total annual cost of infliximab maintenance therapy (administered every 8 weeks) is more than $16,422 per patient [69], and the question has been asked whether infliximab is a cost-effective treatment. Rubenstein and colleagues [70] sought to answer that question by performing a chart review of 79 patients who had CD who had been followed at their institution for up to 3 years before and 1 year after initiation of infliximab therapy to determine if infliximab decreased their health care costs. In this study, decreases of 59%, 59%, and 66%, respectively, were observed in the annual rate of hospitalization, gastrointestinal surgeries, and all surgeries after initiation of infliximab treatment compared with the period before treatment initiation.

Lichtenstein and colleagues [71] examined the effect of maintenance infliximab therapy on hospitalizations, surgeries, and procedures in patients who had fistulizing CD enrolled in the ACCENT II study. Results of this study demonstrated that there was a significant difference ($P < .05$) between the infliximab-treatment and placebo groups in the mean number of CD-related hospitalizations. The 5-mg/kg infliximab maintenance group had a reduction of greater than 50% in the number of hospitalizations and hospitalization days compared with the placebo maintenance group.

Rutgeerts and colleagues [72] reviewed the ACCENT I data and evaluated the rate of hospitalizations and surgeries of patients who had CD and were

treated episodically with infliximab versus those who received scheduled infusions. In the infliximab 5- and 10-mg/kg scheduled-treatment groups, there were significantly fewer CD-related hospitalizations (23 and 24 per 100 patients, respectively) compared with patients in the infliximab episodic-treatment group (38 per 100 patients; $P = .047$ and $P = .023$, respectively, for each comparison). In addition significantly fewer patients in the scheduled-treatment group required CD-related surgery compared with the episodic-treatment group. Scheduled maintenance therapy resulted in approximately half as many hospitalizations and surgeries compared with those required by patients receiving episodic therapy.

Although the cost of infliximab maintenance therapy is indeed significant, the use of infliximab every 8 weeks has been shown to reduce significantly the number of hospitalizations and surgeries in patients who have CD. Because these two areas of health care account for 80% of the direct cost for patients who have CD, the medication cost of infliximab may be offset by an overall cost savings. In a break-even scenario, the indirect and personal benefits of infliximab are substantial enough to merit its use. (The economics of biologic therapy is further discussed elsewhere in this issue.)

SUMMARY

Infliximab has been available in the United States and Europe for more than 6 years, and its use has revolutionized the care of patients who have CD. It is used effectively for both the induction and maintenance of remission in patients who have CD and is efficacious in patients who have steroid-dependent/refractory CD and those who have fistulizing CD. Clinical trials and practice have shown infliximab to be safe, effective, and generally well tolerated. The ACCENT I and ACCENT II trials defined the best dosing and schedule regimens for its administration [32,35].

With up to 30% of patients not responding to infliximab therapy, much attention has been devoted to identifying risk factors that could allow optimization of response rates. Parsi and colleagues [73] and Arnott and colleagues [74] demonstrated that nonsmoking and the concurrent use of immunomodulators are predictors of response to infliximab. Research has also focused on identifying biologic and immunologic markers that may correlate with response to infliximab [75]. To date, *NOD2/CARD15*, anti–*Saccharomyces cerevisiae* antibody (ASCA), and antineutrophil cytoplasmic antibody (ANCA) have not been shown to be predictive of outcome with infliximab treatment for CD [76,77]. Gene polymorphisms also are being studied with the hope that knowing the patient's genotype may help predict the course or severity of the disease, including the presence of extraintestinal manifestations, response to treatments, and susceptibility to toxicities [78]. No single variable, however, has been consistently demonstrated to be a predictor of response to infliximab.

The formation of ATIs in a small number of patients creates a clinical dilemma. ATIs have been associated with an attenuated response or loss of response to the medication over time and the development of both acute

and delayed infusion reactions that occasionally are severe enough to lead to discontinuation of the medication. In such patients physicians are often left to ponder what therapy to try next. Adalimumab, a fully human monoclonal antibody used for treating rheumatologic conditions, has been investigated as an alternate treatment for patients who have CD who, after initially responding to infliximab, experience intolerance or loss of efficacy. Two studies have examined the use of adalimumab in patients who have active CD who had lost response to or developed intolerance to infliximab [79,80]. In both these studies adalimumab was well tolerated and seemed to be a clinically beneficial option for such patients. Confirmation of these findings with ongoing randomized, double-blind, placebo-controlled trials is needed, however.

The limits of conventional treatments for CD can be seen as a positive evolutionary force favoring the development and use of advanced therapies. The acceptance of antimetabolites began with data published a quarter-century ago and became robust in the past 5 to 10 years. Biologic therapy has become the standard of care at a far faster rate. The success seen with infliximab has broadened the acceptance of biologic therapy among professional peers, patients, and pharmaceutical developers. The lessons learned in the years since infliximab's arrival show the importance of long-term data in revealing important toxicities and best practices for maintenance. Tempered by this experience, the short cycle from concept to drug production possible with biologic therapies should bring even more advanced treatments to patients quickly while investigators work to find a cure.

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Infliximab in Fistulizing Crohn's Disease

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Crohn's disease (CD) is a chronic inflammatory disorder that may affect any part of the bowel, from mouth to anus. Three main patterns of phenotypic disease expression have been described: (1) inflammatory, (2) structuring, and (3) fistulizing. Fistulae were first described by Crohn and coworkers [1] in 1932 in their initial description of regional ileitis. Although no perianal lesions were noted by these authors, perianal fistulae were observed in association with CD soon after by Bissell [2]. Fistulae are now recognized as a common and important aspect of this disease. The treatment of Crohn's fistulae has improved greatly over the last decade as new medical therapies, especially infliximab, have been developed. This article reviews the current knowledge of fistulizing CD, focusing primarily on its medical management.

BACKGROUND

Classification

Fistulae can be classified into two main groups: internal and external. Internal fistulae can be further subdivided into two types: those that occur between intestinal structures, such as enteroenteric, enterocolic, and gastrocolic; and those that occur between the intestine and other organs, such as rectovaginal, enterovesical, and abdominal wall [3].

External fistulae represent a connection from some part of the bowel to the outside world by the skin and include enterocutaneous and perianal fistulae. Perianal fistulae, the most common type of external fistula, historically have been classified in a variety of ways. The most clinically useful way to classify fistulae was recently proposed by the American Gastroenterological Association in a position statement and technical review on perianal CD [4,5]. They stratify perianal fistulae

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into two groups: simple and complex. Simple fistulae are low (ie, below the dentate line) and have a superficial, low intersphincteric, or low transsphincteric origin. These fistulae also have a single external opening, have no associated pain or fluctuation to suggest an abscess, and have no evidence of a rectovaginal fistula or anorectal stricture. Complex fistulae, however, are high in origin (high intersphincteric, high transsphincteric, or suprasphincteric); may have multiple external openings; may have associated pain or fluctuation to suggest an abscess; and may have evidence of a rectovaginal fistula or anorectal stricture. The distinction between the two types of perianal fistula is clinically important, not only because the management varies, but also because several studies have demonstrated higher rates of healing with simple fistulae [6–9].

Pathogenesis

The transmural nature of the inflammation that typifies CD predisposes patients to fistula formation. Internal fistulae seem to arise as the inflammatory process in the bowel extends to adjacent organs [10]. Although the pathogenesis of perianal fistulae is not known precisely, two mechanisms seem plausible [11]. Perianal fistulae may develop locally as deep penetrating ulcers in the anus or rectum, which then extend over time as feces is forced into the ulcers during defecation [12]. Alternatively, these fistulae may develop after anal gland infections or abscesses [13]. Because some of the anal glands penetrate into the intersphincteric space, infection in this space can readily extend to the external anal sphincter or skin.

Natural History

The reported incidence of fistulae in CD patients ranges from 17% to 43% in referral-center–based case series [14–23]. Only two population-based studies examining the natural history of Crohn's fistulae have been published to date [24,25]. The first, a study by Hellers and coworkers [24], included 826 patients diagnosed with CD in Stockholm County, Sweden, from 1955 to 1974 and observed a 23% cumulative incidence of perianal fistulae. The authors noticed that the frequency of perianal fistulae increased as the inflammatory disease became more distal, with a 12% incidence in ileal disease, 15% in ileocolonic disease, 41% in colonic without rectal disease, and 92% in colonic with rectal disease. More recently, Schwartz and coworkers [25] examined 176 patients diagnosed with CD in Olmsted County, Minnesota, from 1970 to 1993 and found a cumulative incidence of at least one fistula (at any site) of 21% at 1 year, 26% at 5 years, 33% at 10 years, and 50% at 20 years. The corresponding cumulative incidences of at least one perianal fistula were 12% at 1 year, 15% at 5 years, 21% at 10 years, and 26% at 20 years. Taken collectively, fistulae were located as follows: 54% perianal, 24% enteroenteric, 9% rectovaginal, 6% enterocutaneous, 3% enterovesical, and 3% entero–intra-abdominal. Interestingly, 45% of patients developed a perianal fistula before or at the time of diagnosis of CD, an observation first noted by Gray and coworkers in 1965 [26] and also seen in the study by Hellers and coworkers

[24]. This observation highlights the frequent difficulties encountered in attempting to diagnose CD in patients with isolated perianal disease.

The clinical course of internal fistulae has not been well studied. Although these fistulae do not always produce symptoms, they are thought by many experts in the field to be indicative of a more aggressive subtype of CD and often require urgent and repeated surgical intervention [3]. The clinical course of perianal fistulae depends somewhat on their complexity. Simple fistulae may heal spontaneously in up to 50% of cases [18,27], whereas complex fistulae rarely heal spontaneously [10]. A number of studies have demonstrated that simple perianal fistulae tend to heal more completely and recur less than complex fistulae [7,9,27–29].

Diagnosis

Internal fistulae are most easily and reliably detected on barium studies or CT, or MRI, regardless of whether or not they are suspected clinically. In the case of perianal fistulae, because healing rates seem to decrease when fistulae transform from simple to complex, it is tantamount to recognize and treat them as soon as symptoms manifest themselves. Fistula location and extent must be accurately ascertained before commencing therapy. Unfortunately, digital rectal examination alone is not sufficient in this capacity, with accuracy as low as 62% [30]. Fortunately, a variety of other modalities exist, including fistulography, pelvic CT, pelvic MRI, anorectal endoscopic ultrasound (EUS), and examination under anesthesia (EUA). Fistulography, which may cause significant patient discomfort and more importantly may disseminate septic fistula content, has a reported diagnostic accuracy of 16% to 50%, which is too low to be clinical useful [31–35]. Similarly, CT, with its limited diagnostic accuracy of 24% to 60%, is also not particularly useful [36–42]. Pelvic MRI, however, represents a vast improvement with a reported diagnostic accuracy of 76% to 100% and is often used to delineate anorectal and pelvic anatomy [43–51]. Anorectal EUS is also a clinically useful diagnostic modality with diagnostic accuracy ranging from 56% to 100% [42,50,52–57]. Of note, both pelvic MRI and anorectal EUS have been found to change surgical management in 10% to 15% of cases [45–51,57]. EUA performed by an experienced colorectal surgeon has long been considered the gold standard for diagnosis of perianal fistulae in patients with Crohn's disease. This view has recently been challenged by Schwartz and coworkers [50], however, who compared EUA, MRI, and EUS in a prospective blinded study of 34 patients with suspected Crohn's perianal fistulae. In this study, a consensus gold standard was determined for each patient. The authors observed a diagnostic accuracy exceeding 85% for all three modalities, specifically 91% for EUA and EUS, and 87% for MRI. Of note, when any two of the tests were combined, diagnostic accuracy increased to 100%. Caution must be exercised, however, because this study was performed at a tertiary referral medical center with significant expertise in these imaging modalities. Similar results may not necessarily be reproduced in community medical centers.

MEDICAL TREATMENT

5-Aminosalicylic Acid Derivatives

Although modestly efficacious in inducing remission in patients with mild-to-moderate CD, the treatment of Crohn's fistulae with 5-aminosalicylic acid derivatives has never been studied in controlled trials. They cannot be recommended for the treatment of fistulizing CD.

Corticosteroids

There are no controlled studies evaluating the use of steroids in the management of Crohn's fistulae. Unfortunately, neither the National Cooperative Crohn's Disease trial nor the European Cooperative Crohn's Disease trial provided data on response in the subgroup of patients with fistulae. Two large uncontrolled studies have shown that corticosteroid use may actually be detrimental to patients with fistulizing CD, however, because it was associated with higher rates of surgical intervention [58,59]. A recent retrospective case-control study of 432 patients with CD studied risk of intra-abdominal or pelvic abscess with systemic corticosteroid use during the previous 3 months [60]. The authors found a significant ninefold increased risk of intra-abdominal or pelvic abscess in patients with perforating CD who had received systemic corticosteroids during the prior 3 months (adjusted odds ratio = 9.03; 95% CI, 2.40–33.98). In patients with relapsed active disease, they also reported a significant ninefold increased risk of abscess in patients receiving systemic steroids in the 3 months before presentation (unadjusted odds ratio = 9.31; 95% CI, 1.03–83.91). For these reasons, corticosteroids should generally (except in some very unusual circumstances) not be used in patients with active fistulizing CD.

Antibiotics

Although antibiotics are the most commonly used medication for the treatment of fistulae in CD, there are no controlled data indicating that these agents are effective in this regard. The use of antibiotics in fistulizing CD is based on a number of uncontrolled case series, each with a small number of patients [61–70]. Metronidazole, the most commonly used antibiotic, was first discovered in 1975 to have possible efficacy by Ursing and Kamme [61], who reported perianal fistula closure in three patients. Five years later, Bernstein and coworkers [62] treated 21 consecutive patients with perianal Crohn's fistulae with metronidazole at a dose of 20 mg/kg/d and observed clinical improvement in all patients, fistula closure in 83%, and complete healing in 56%. These responses typically occurred within 6 to 8 weeks of commencement of therapy. In 1982, the same group published a follow-up study, comprised of 17 of the 21 original patients and nine additional consecutive patients, and found that dosage reduction was associated with relapse in all patients [64]. Rapid healing was noted in all patients, however, on readministration of metronidazole. Although efficacious in the induction of improvement, metronidazole is limited in that maintenance therapy is often required. Three other small uncontrolled studies have also observed efficacy with metronidazole in fistulizing CD with fistula closure rates of 40% to 50%, but a high rate of relapse after cessation of therapy

was seen in one of these studies [63,65,66]. The typical dose of metronidazole in the treatment of fistulizing CD ranges from 750 to 1500 mg/d. Adverse events associated with metronidazole are quite common, often leading to intolerance and discontinuation of the drug, and include a distal sensory neuropathy with paresthesia, nausea, dyspepsia, fatigue, glossitis, metallic taste, and a disulfiram-like reaction to alcohol ingestion [71].

Given that adverse events are commonly problematic with metronidazole, ciprofloxacin began to be used in the late 1980s and early 1990s to treat Crohn's fistulae [67–70]. The first report of ciprofloxacin use in this setting was by Turunen and coworkers [67], who studied eight patients with severe perianal disease and one patient with enterocutaneous fistula refractory to metronidazole. In this study, in which patients were given 1000 to 1500 mg/d of ciprofloxacin for 3 to 12 months, the authors found that all patients demonstrated initial improvement, but 50% continued to have persistent drainage, which required surgical intervention in several patients. As with metronidazole, relapses were common on cessation of therapy, but improvement was seen on reinstitution of therapy in most cases. A subsequent study, published only in abstract form by Wolf [68], noted improvement in four out of five patients with severe perianal disease within 5 weeks of treatment. Combination therapy with ciprofloxacin and metronidazole has been examined by Solomon and coworkers [69] in a retrospective study of 14 patients. They observed improvement in nine patients and fistula closure in three patients within 12 weeks, but like previous antibiotic studies, they also reported that relapse was the norm following discontinuation of therapy. The typical dose of ciprofloxacin in the treatment of fistulizing CD ranges from 1000 to 1500 mg/d. Adverse events with ciprofloxacin are uncommon and include headache, nausea, diarrhea, rash, and spontaneous tendon rupture [72,73].

To date, there has been no comparative study published comparing metronidazole and ciprofloxacin in the treatment of fistulizing CD. There is now a trial ongoing evaluating metronidazole versus ciprofloxacin versus placebo for Crohn's fistula funded by the Crohn's and Colitis Foundation of America.

6-Mercaptopurine and Azathioprine

No controlled trials examining fistula healing with 6-mercaptopurine (6-MP) or azathioprine as a primary end point have ever been published. In the very first publication documenting use of azathioprine in CD, Brooke and coworkers [74] reported that all six patients with fistulizing disease who had received azathioprine demonstrated marked clinical improvement in their fistulae. Since then, five randomized controlled trials, which investigated healing of fistulae as a secondary end point, have been published (Table 1) [75–79]. The studies used improvement or complete healing of fistulae as the outcome measure. With the exception of the trial by Present and coworkers [79], the studies had very few patients with fistulizing disease. The studies were quite heterogeneous with respect to duration of therapy; there was also some variability in medication used and dosage. Three of the five trials observed higher rates of

Table 1
Randomized controlled trials for treatment of fistulizing Crohn's disease with 6-MP or azathioprine

Author, year	N	Drug, dose	Rx time	Response drug (%)	Response placebo (%)	*P* value
Willoughby et al, 1971 [75]	3	Azathioprine, 2 mg/kg/d	24 wk	0/2 (0)	0/1 (0)	NR
Rhodes et al, 1971 [76]	6	Azathioprine, 2 mg/kg/d	2 mo	2/4 (50)	0/2 (0)	NR
Klein et al, 1974 [77]	10	Azathioprine, 3 mg/kg/d	4 mo	4/5 (80)	2/5 (40)	NR
Rosenberg et al, 1975 [78]	5	Azathioprine, 2 mg/kg/d	26 wk	0/4 (0)	1/1 (100)	NR
Present et al, 1980 [79]	46	6-MP, 1.5 mg/kg/d	1 y	16/29 (55)	4/17 (24)	NR

Abbreviations: 6-MP, 6-mercaptopurine; N, number of patients; NR, not reported; Rx, treatment.

fistula improvement with 6-MP or azathioprine [76,77,79]. Of note, the study by Present and coworkers [79] observed a 31% rate of complete closure of the fistulae in the group receiving 6-MP versus 6% for the placebo group. A meta-analysis of these five trials reported an overall response rate (defined as improvement or complete healing) in 54% of patients treated with 6-MP or azathioprine compared with 21% in patients treated with placebo [80]. The corresponding pooled odds ratio for fistula healing with 6-MP or azathioprine was 4.44 (95% CI, 1.50–13.20). When interpreting the results of this meta-analysis, it is important to keep in mind that most of the fistulous cases (46 [66%] of 70) were derived from a single study conducted at a single center [79]. The results of the meta-analysis were driven largely by that one study. Moreover, as mentioned previously, fistula healing was not a primary end point for any of the individual trials.

In addition, two uncontrolled case series, one in adults and one in children, have been published [81,82]. The adult series, by Korelitz and Present [81], treated 34 patients with 6-MP at a dose of 1.5 mg/kg/d with various types of fistulae, including perianal (18 patients); abdominal wall (eight patients); enteroenteric (seven patients); rectovaginal (six patients); and vulvar (two patients). Complete fistula closure was achieved in 39% of patients, with an additional 26% showing improvement. This study also underscored the importance of maintenance therapy. Fistulae remained closed for 1 to 5 years in 46% of patients (6 out of 13) who remained on 6-MP, and relapses tended to occur within 2 weeks to 9 months after discontinuation of the drug. Healing was once again achieved on readministration of 6-MP. Furthermore, the authors noted that although all types of fistulae responded to 6-MP, abdominal wall and enteroenteric fistulae responded particularly well.

The combination of azathioprine and antibiotics has also been investigated. Recently, Dejaco and coworkers [83] published a prospective, open-label study

evaluating the use of an 8-week course of ciprofloxacin or metronidazole as a bridge to azathioprine in the treatment of 52 patients with perianal fistulae. In this trial, 17 patients had been taking azathioprine before the start of the study, and another 14 patients were initiated on azathioprine after the 8-week course of antibiotics. At week 8, 50% of patients had improved and 25% had achieved complete healing. At week 20, improvement was seen overall in 35% of patients, with complete healing in 18%. Patients who received azathioprine were significantly more likely to achieve response at week 20 than those who did not receive azathioprine (48% versus 15%, $P = .03$). More evidence is provided that maintenance therapy is critical to continued fistula healing.

The cost-utility of the combination of metronidazole and 6-MP with or without infliximab has been studied by Arseneau and coworkers [84], who designed a 1-year Markov model for therapy of perianal Crohn's fistulae. They observed that all treatment strategies had similar effectiveness, but strategies involving infliximab were much more expensive. Their conclusion was that the incremental benefit of infliximab may not justify the higher cost over a 1-year period. This study has, however, been critiqued by many individuals and a recent prospective randomized placebo controlled trial (ACCENT II) demonstrated cost saving in patients maintained on maintenance infliximab when compared with those who did not receive maintenance therapy (discussed later). Metronidazole combined with 6-MP seems to have the highest initial cost-utility in the treatment of fistulizing perianal CD.

Typical doses of 6-MP and azathioprine used in clinical trials were 1 to 1.5 mg/kg/d and 2 to 3 mg/kg/d, respectively. Currently, there is some debate as to whether dosing according to level of the active metabolites, the 6-thioguanine nucleotides, should be used routinely. A recent meta-analysis has demonstrated that higher 6-thioguanine nucleotide levels (especially $\geq$230–260 pmol/10^8 red blood cells) were associated with clinical remission [85]. Adverse events are common with 6-MP and azathioprine, occurring in 9% to 15% of patients, and include allergic reactions; bone marrow suppression (especially leukopenia); pancreatitis; infection; hepatotoxicity; non-Hodgkin's lymphoma; and other gastrointestinal side effects (nausea, vomiting, and abdominal pain) [80,86,87].

Methotrexate

Methotrexate has been shown to be effective in the induction and maintenance of remission of CD in several controlled trials. Unfortunately, these studies did not address fistulizing disease. To date, only two retrospective case series have been published which examined the use of methotrexate for Crohn's fistula [88,89]. The first, by Vandeputte and coworkers [88], analyzed 20 patients, 8 of whom had fistulae, refractory to azathioprine and requiring continuous corticosteroid treatment. The authors reported improvement in 70% of patients overall with parental methotrexate within 12 weeks but did not specify the outcome of the patients with fistulae. The other series, by Mahadevan and coworkers [89], included 37 courses of intramuscular or oral methotrexate

given to 33 patients, 16 of whom had fistulae and were intolerant or refractory to 6-MP. Complete fistula closure was achieved in 25% with another 31% showing improvement. Similar to other medications, fistulae often recurred when the dose of intramuscular methotrexate was decreased or when the route of administration was changed to oral. Methotrexate may represent a reasonable alternative for patients who fail or cannot tolerate 6-MP or azathioprine, and long-term maintenance therapy is likely necessary; however, prospective randomized placebo-controlled trials are still needed to evaluate formally the efficacy of methotrexate for fistulizing CD. The initial dose of methotrexate suggested is 25 mg intramuscularly every week. Concurrent administration of folate is advocated to lessen nausea. Adverse events are common and include hepatic fibrosis, bone marrow suppression, hypersensitivity pneumonitis and pulmonary fibrosis, nausea, and teratogenicity [90,91].

Cyclosporine A

There are no controlled trials documenting efficacy of cyclosporine for the treatment of fistulizing CD. To date, 10 case series, with a total of 64 patients, assessing cyclosporine in Crohn's fistula have been published [92–101]. The largest series, by Present and Lichtiger [96], looked at 16 patients with various types of Crohn's fistulae (perianal, rectovaginal, and enterocutaneous) treated with intravenous cyclosporine at a dose of 4 mg/kg/d and observed improvement in 88% with complete fistula closure in 44%. The mean time to response was rather short at just over 7 days. The authors noted that 36% of patients relapsed when converted to oral cyclosporine. Taken collectively, the 10 case series showed an initial response rate of fistulizing CD to intravenous cyclosporine of 83% at doses of 2.5 to 5 mg/kg/d (mostly 4 mg/kg/d). The overall rate of fistula recurrence after discontinuing oral cyclosporine was 62%, however, and most authorities use cyclosporine as a bridge to other maintenance therapies, such as 6-MP or azathioprine [3,10,11]. The recommended initiation intravenous dose of cyclosporine is 2 mg/kg/d for 1 week, followed by oral formulation, typically 6 to 8 mg/kg/d, all dosed by levels. A recent study has demonstrated that initiation of therapy with cyclosporine using 2 mg/kg demonstrated similar efficacy compared with cyclosporine 4 mg/kg continuous infusion [102]. Adverse events are common and include paresthesia, hirsutism, hypertension, tremor, renal insufficiency, headache, opportunistic infections, gingival hyperplasia, seizures, and hepatotoxicity [90,103].

Tacrolimus

Several uncontrolled case series, with a total of 16 patients with Crohn's fistulae, have suggested that tacrolimus may have efficacy in the management of fistulizing disease [104–107]. The only controlled trial of tacrolimus for fistulizing CD is a randomized, double-blind, placebo-controlled study of 48 patients with perianal or enterocutaneous fistulae by Sandborn and coworkers [108]. In this study, patients received oral tacrolimus at 0.2 mg/kg/d or placebo for 10 weeks. The primary end point, fistula improvement (defined as closure of $\geq$50% of draining fistulae and maintenance of closure for at least 4 weeks), occurred

in 43% of patients receiving tacrolimus, compared with 8% of patients on placebo ($P = .004$). There was no difference in the secondary end point, fistula remission (defined as closure of all fistulae and maintenance of that closure for at least 4 weeks), between the two groups (10% of tacrolimus-treated patients versus 8% of placebo-treated patients). Of note, 38% of patients treated with tacrolimus developed increases in serum creatinine to ≥1.5 mg/dL, necessitating dose reduction. Recently, Gonzalez-Lama and coworkers [109] conducted a small, uncontrolled, prospective, open-label study of long-term oral tacrolimus at a dose of 0.1 mg/kg/d in 10 patients with Crohn's fistulae refractory to all conventional therapy, including infliximab. Patients in the study had perianal, enterocutaneous, and rectovaginal fistulae. The authors found that after 6 to 24 months of follow-up, 50% of patients achieved complete response and an additional 40% showed improvement. Importantly, no relapses and no cases of nephrotoxicity occurred throughout the follow-up period. In addition to nephrotoxicity, other adverse events associated with tacrolimus include headache, insomnia, paresthesia, tremor, and leg cramps [108].

Infliximab

Given that inflammation in CD is associated with high levels of tissue tumor necrosis factor-α (TNF-α) expression, therapies directed against this cytokine have become a recent focus of interest. Infliximab, a chimeric (75% human, 25% murine) IgG1 monoclonal antibody directed against TNF-α, is the prototype anti–TNF-α agent and has now become the cornerstone in medical therapy of fistulizing CD. Several uncontrolled studies have shown efficacy of infliximab in this regard [110–112]. Infliximab has also been shown to be efficacious in the treatment of Crohn's fistula in two multicenter randomized, double-blind, placebo-controlled trials [113,114]. The first, by Present and coworkers [113], randomized 94 patients with draining abdominal (10% of patients) or perianal (90% of patients) fistulae to placebo, infliximab at a dose of 5 mg/kg, or infliximab at 10 mg/kg, administered intravenously at weeks 0, 2, and 6. The primary end point was a reduction in the number of draining fistulae by ≥50%, which was maintained for at least 4 weeks, and a secondary end point was closure of all fistulae. The authors found that the primary end point was achieved in 68% of patients who received infliximab at 5 mg/kg and 56% of patients who received infliximab at 10 mg/kg, compared with 26% of patients who received placebo ($P = .002$ and $P = .02$, respectively). Closure of all fistulae was achieved in 55% of patients who received infliximab at 5 mg/kg and 38% of patients who received infliximab at 10 mg/kg, compared with only 13% of patients who received placebo ($P = .001$ and $P = .04$, respectively). The median time to response was 14 days for infliximab-treated patients versus 42 days for patients assigned to placebo, and most infliximab-treated patients achieved fistula closure before the third infusion. Eleven percent of infliximab-treated patients developed a perianal abscess, possibly resulting from premature closure of the cutaneous end before closure of the rest of the fistula tract. The overall rates of infection did not differ, however, between the infliximab and placebo groups.

In the study by Present and coworkers [113], the median duration of response was 3 months, suggesting that, similar to the treatment of Crohn's fistula with other medications, maintenance therapy may be required. In addition, because the treatment of luminal CD with infliximab often necessitates maintenance therapy, it should not come as a surprise that maintenance infliximab may be of benefit in the management of fistulizing CD. The other multicenter, randomized, double-blind, placebo-controlled trial of infliximab for Crohn's fistula, the ACCENT II trial, reported by Sands and coworkers [114], followed 282 patients with draining perianal, abdominal, and rectovaginal fistulae. All patients were induced with infliximab at 5 mg/kg at weeks 0, 2, and 6, and response, defined as a reduction in the number of draining fistulae by $\geq$50% for at least 4 weeks, was achieved in 195 patients (69%), similar to the induction response rate reported by Present and coworkers [113]. At week 14, these 195 responders were then randomly assigned to receive infusions of either infliximab, 5 mg/kg, or placebo every 8 weeks until week 54. The primary end point was time to loss of response. The authors observed a median time to loss of response of 40 weeks in infliximab-maintained patients versus 14 weeks in placebo-assigned patients ($P = .001$). Overall, 42% of patients in the infliximab group had a loss of response, compared with 62% in the placebo group. At week 54, 46% of patients treated with infliximab still had a response, versus 23% of patients treated with placebo ($P = .001$). In addition, at week 54, 36% of patients in the infliximab group had a complete absence of draining fistulae, compared with 19% in the placebo group ($P = .009$). Sands and coworkers [115] subsequently performed a post hoc analysis of the ACCENT II data looking at the efficacy of infliximab induction and maintenance in the subset of women with rectovaginal fistulae. Twenty-five of the original 138 women had a total of 27 draining rectovaginal fistulae at baseline. At week 14, 64% of these 25 women had responded and were then randomized to receive infliximab or placebo maintenance therapy. The authors reported a median time to loss of response of 46 weeks for the infliximab group versus 33 weeks in the placebo group.

The social impact of infliximab in patients with active fistulizing CD has also been investigated in two recent studies. Cadahia and coworkers [116] were interested in the effect of infliximab induction treatment on health-related quality of life, and they conducted a prospective observational study of 25 patients who received three-dose induction infliximab therapy for single or multiple draining abdominal or perianal fistulae. The authors found that health-related quality of life, as measured by the SF-36, demonstrated significant improvement in the physical domain after 4 and 10 weeks. In addition, a significant increase in Inflammatory Bowel Disease Questionnaire score was seen after 4 weeks. More recently, Lichtenstein and coworkers [117] evaluated the impact of infliximab maintenance therapy on the number of hospitalizations, surgeries, and procedures in patients with fistulizing CD. Using data from the ACCENT II trial, they revealed that compared with patients who received placebo, patients who received maintenance infliximab had significantly fewer number

of mean hospitalization days (0.5 versus 2.5 days); hospitalizations (0.11 versus 0.31); total surgeries and procedures (65 versus 126); inpatient surgeries and procedures (7 versus 41); and major surgeries (2 versus 11).

Mechanistically, infliximab's effects on mucosal cytokine profiles may predict which patients with fistulizing CD will relapse. Agnholt and coworkers [118] recently collected tissue samples for cytokine analysis from 26 patients with Crohn's fistulae. They observed that fistula healing was associated with decreased production of TNF-α, interferon-γ, and interleukin-10, whereas relapse was associated with increased production of interferon-γ.

Despite all of its reported success, the use of infliximab may not obviate the need for surgical management of Crohn's fistulae in many cases. Poritz and coworkers [119] retrospectively examined surgical rates in patients treated with infliximab for fistulizing CD at a single institution. Among the 26 patients with various types of fistulae, 46% experienced a partial response to infliximab, and an additional 23% had fistula closure. A total of 54% of patients overall still required surgery after infliximab therapy, however, and another 23% continued to open fistulous drainage but refused surgery. Of note, none of the patients with either enterocutaneous or peristomal fistulae were healed with infliximab treatment. Moreover, infliximab therapy may not be the most cost-effective initial strategy in the management of Crohn's perianal fistulae, according to the cost-utility analysis performed by Arseneau and coworkers [84]. Compared with the combination of 6-MP and metronidazole, any initial intervention involving infliximab resulted in an increase in incremental cost-utility by more than $350,000 per quality-adjusted life year, caused exclusively by the high cost of infliximab.

The effectiveness of infliximab in combination with other medical therapies for fistulizing CD has also been investigated in several studies [120–122]. West and coworkers [120] conducted a double-blind, placebo-controlled trial of ciprofloxacin overlapping with infliximab in patients with perianal Crohn's fistulae. In this study, 24 patients were randomized to receive either ciprofloxacin at 1000 mg/d or placebo for 12 weeks in addition to infliximab at 5 mg/kg at weeks 6, 8, and 12. Patients were followed for 18 weeks, and the primary end point was reduction in the number of draining fistulae by $\geq$50%. The authors reported that 73% of the ciprofloxacin-treated patients responded, compared with 39% in the placebo group. One caveat is that the response rate to infliximab alone was much less than in other infliximab studies, in which at least 60% of patients responded. Infliximab has also been evaluated in combination with immunomodulator therapy. Ochsenkühn and coworkers [121] performed an uncontrolled pilot study of long-term 6-MP (at 1 mg/kg/d) or azathioprine (at 2–2.5 mg/kg/d) in combination with induction infliximab in 16 patients. They found that 75% of patients achieved complete fistula closure, which persisted for more than 6 months (median time of 10 months). As seen previously, the median time to fistula closure was 14 days. A similar uncontrolled pilot study by Schröder and coworkers [122] followed 12 consecutive patients with Crohn's fistulae intolerant or resistant to azathioprine. Patients

were treated with induction infliximab and long-term methotrexate at 20 mg/wk (intravenously for 6 weeks, followed by oral thereafter). The authors observed that 33% of patients experienced complete fistula closure for at least 6 months (median 13 months), and 25% had a partial response. Although providing a suggestion of efficacy of combination therapy for treatment of fistulizing CD, controlled trials have yet to be performed.

The combination of infliximab with surgical intervention in the treatment of Crohn's perianal fistulae has also been recently assessed in several studies [7,8,123,124]. Regueiro and Mardini [7] retrospectively analyzed 32 consecutive patients with perianal Crohn's fistulae, all of whom had received at least three induction doses of infliximab and some of whom had additionally undergone an EUA with seton placement before infliximab treatment. Response was defined as complete closure and cessation of drainage from the fistula. They found that compared with patients treated with infliximab alone, patients who had a preinfusional EUA with seton placement had a significantly higher rate of initial response (100% versus 83%, $P = .014$); lower rate of recurrence (44% versus 79%, $P = .001$); and longer time to recurrence (13.5 months versus 3.6 months, $P = .0001$). Another study, by van der Hagen and coworkers [123] compared 10 patients treated with seton placement followed by infliximab with 7 patients treated with surgery alone in a retrospective review of consecutive patients with complex perianal fistulae. After a median follow-up of 19 months, all patients achieved fistula healing. Fistula recurrence was seen in one patient (10%) in the combined therapy group versus two patients (29%) in the surgery-alone group. Two other case series have also documented favorable rates of fistula healing with seton placement followed by induction and maintenance infliximab, with complete and partial healing rates of 67% and 19%, respectively, in one study [8] and 47% and 53%, respectively, in the other [124].

Adverse events with infliximab treatment are common and include infusion reactions; delayed-type hypersensitivity reactions; formation of human antichimeric antibodies (currently known as "antibodies to infliximab"); formation of antinuclear and anti–double-stranded DNA antibodies; and drug-induced lupus-like reactions [125–127]. In addition, infectious complications seem to be increased, but serious infections, such as pneumonia, sepsis, tuberculosis, and opportunistic infections, including listeriosis, aspergillosis, histoplasmosis, coccidiomycosis, and *Pneumocystis carinii* pneumonia, occur only rarely [128–132]. Finally, there are isolated case reports of hepatic necrosis and non-Hodgkin's lymphoma in patients treated with infliximab, although it has not been determined whether these events were the direct consequence of infliximab therapy.

Other Anti–Tumor Necrosis Factor-α Agents

Several other anti–TNF-α medications have shown promise in the treatment of fistulizing CD and may provide an alternative option for patients in whom infliximab either is not tolerated, has lost efficacy, or was never effective. Adalimumab, a fully human IgG1 monoclonal antibody, was investigated by Sandborn and coworkers [133] in a recent pilot study of 24 patients with

CD who had lost responsiveness or developed intolerance to infliximab. In this 12-week, uncontrolled trial, patients received 80 mg of subcutaneous adalimumab at week 0, followed by 40 mg every other week starting at week 2. Nine patients in the study had fistulizing disease with open and draining perianal or enterocutaneous fistulae. The authors observed fistula improvement, defined as a reduction in the number of draining fistulae by $\geq$50%, in two patients (22%) at week 2; four patients (44%) at week 4; and five patients (56%) at week 12. Complete fistula closure was achieved in one patient (11%) at week 2; three patients (33%) at week 4; and three patients (33%) at week 12. Overall, among the 24 patients, 71% experienced adverse events, which were serious in only two patients (8%) and required withdrawal in one patient with new-onset seizure. Reported adverse events included upper respiratory infection, headache, bronchitis, rash, fatigue, arthritic pain, abdominal pain, back ache, nausea, perianal abscess, numbness, and injection site reaction. Because this study was not placebo-controlled, however, it is difficult to say which of these adverse reactions can be attributed directly to adalimumab.

CDP571, a humanized (95% human, 5% murine) IgG4 monoclonal antibody, has been also been assessed for efficacy in the treatment of Crohn's fistulae in two multicenter, randomized, double-blind, placebo-controlled trials [134,135]. The first study, by Feagan and coworkers [134], published only in abstract form, treated 71 patients with steroid-dependent CD with intravenous CDP571 at 20 mg/kg or placebo at week 0, followed by a second infusion of CDP571 at 10 mg/kg or placebo at week 8. At week 16, among the subgroup of patients with draining perianal fistulae, fistula closure was achieved in 25% of patients who received CDP571, compared with none in the placebo group. The other study, by Sandborn and coworkers [135], followed 169 patients for 24 weeks, during which patients received an initial infusion of CDP571 at either 10 mg/kg or 20 mg/kg or placebo, followed by CDP571 at 10 mg/kg or placebo every 8 to 12 weeks. This study included 37 patients with open perianal or enterocutaneous fistulae and reported that 50% of patients treated with CDP571 achieved fistula closure versus 15% of patients who received placebo. Adverse events caused by CDP571 include infusion reactions, formation of anti-idiotype antibodies, development of new antinuclear or anti–double-stranded DNA antibodies, insomnia, pruritus, and rash [134,135].

Thalidomide has also been preliminarily evaluated in the treatment of fistulizing CD in two open-label pilot studies [136,137]. The first study, by Ehrenpreis and coworkers [136], enrolled 22 patients with refractory CD to receive oral thalidomide at 200 or 300 mg/day for 12 weeks. At week 4, of the 13 patients with fistulae, nine patients (69%) responded; three patients (23%) achieved remission; and two patients (15%) had closure of all fistulae. Nine patients with fistulizing disease completed the 12 weeks of treatment. Of these nine patients, all (69%) were responders; six patients (46%) achieved remission; and five patients (38%) had complete closure of all fistulae. The other pilot study, by Vasiliauskas and coworkers [137], treated 12 patients with steroid-dependent CD with 50 or 100 mg/day of thalidomide for 12 weeks. Of the

six patients with active perianal fistulae at the time of entry into the study, five (83%) had improvement in symptoms after 4 weeks. Four of these six patients with fistulizing disease completed 12 weeks of treatment. Fistula closure was achieved in one patient (17%) at week 12, with improvement in another two patients (33%). Adverse events are common with thalidomide therapy and include severe somnolence, peripheral neuropathy, teratogenicity, peripheral edema, constipation, seborrheic dermatitis, hypertension, muscle spasm, and diffuse rash [136,137].

Novel Therapies

A variety of other therapies for fistulizing CD have been suggested to be of possible benefit in uncontrolled case series or anecdotally. These include elemental diets, bowel rest with total parental nutrition, mycophenolate mofetil, granulocyte-colony stimulating factor, hyperbaric oxygen, and coagulation factor XIII [138–158]. Controlled trials are required, however, before any of these modalities can be recommended for routine use.

SURGICAL TREATMENT

A complete discussion of the surgical management of Crohn's fistulae is beyond the scope of this article. Because surgery plays an essential role in this setting, a brief summary of surgical treatment options is provided. Most often, a combination of medical and surgical therapies is required, and the gastroenterologist and surgeon should work together closely in each patient's case. Proper treatment of fistulizing CD relies heavily on several factors. Most importantly, fistula anatomy must be accurately defined, specifically identifying the origin and terminus of the fistula tract. Scrupulous attention should also be paid to searching for the presence of abscess formation, because abscesses often require drainage. In addition, the location and extent of bowel inflammation must be delineated, because this information has treatment implications.

Internal Fistulae

Internal fistulae are often a harbinger of an aggressive phenotypic expression of CD. Unfortunately, controlled data are lacking with respect to the efficacy of medical treatment on healing of internal fistulae. The presence of abscess formation must be aggressively sought. Small abscesses may respond to antibiotics alone, but larger ones almost always require drainage, either percutaneous or surgical, in addition to antibiotic therapy. The presence and degree of intestinal inflammation in the area of the internal fistula should also be determined. Medical agents most often used to treat luminal inflammatory disease in this setting include immunomodulators and infliximab. It is not uncommon, however, for these modalities to fail in controlling the inflammation. In addition, medical therapy is frequently unsuccessful in healing or closing the concomitant internal fistulae. Surgery, involving resection of the diseased segment of the bowel along with fistula resection, is often a necessity for patients with symptomatic

disease. Asymptomatic internal fistulae, however, do not necessarily warrant surgical intervention. In fact, there is a paucity of data assessing the impact of any treatment, medical or surgical, on the natural history of asymptomatic internal fistulae.

Perianal Fistulae

The most important step in the management of Crohn's perianal fistulae is their accurate diagnosis through EUA, pelvic MRI, anorectal EUS, or a combination of these. Once diagnosed, management decisions hinge upon two factors: the type of fistula (simple versus complex) and the presence or absence of active proctitis.

Simple fistulae with no associated proctitis can be effectively treated with fistulotomy, which involves simply laying open the fistula tract. To date, 21 surgical series have been published that addressed healing rates of simple Crohn's perianal fistulae with fistulotomy [20,21,27,159–174]. The three studies, which included only patients without active proctitis, documented healing rates of 90% to 100% [21,159,168]. The other 18 studies, which included some patients with active proctitis, revealed a wide range of healing rates from 8% to 100%, with healing rates exceeding 80% in 10 of the studies. A surgical alternative to fistulotomy in patients with simple fistulae without active proctitis is an endorectal advancement flap, which entails incising a flap of tissue around the internal opening of the fistula tract, excising the internal opening, and then pulling the flap down over the opening to cover [175]. Success rates with this technique are similar to those with fistulotomy. It is unclear at the present time, however, whether surgery is the preferred treatment modality for simple perianal Crohn's fistulae. Medical treatment options, such as antibiotics, immunomodulators, and infliximab, have also been shown to be effective. Many surgeons advocate fistulotomy in patients who fail to respond to an initial course of antibiotics. Unfortunately, controlled data are lacking with respect to the use of antibiotics, immunomodulators, and surgical intervention in this capacity, and infliximab is associated with a high rate of abscess formation and high costs. In addition, there are no studies directly comparing one therapeutic modality with another. A combined medical and surgical strategy is also an option and may even be more efficacious than either modality alone, as discussed previously in two studies combining infliximab with EUA and seton placement [7,123].

Active proctitis changes the management of simple fistulae slightly, because active rectal inflammation is associated with poor wound healing in patients who undergo fistulotomy [168]. More importantly, a nonhealing wound following fistulotomy may necessitate proctectomy in certain patients. For these reasons, most surgeons advocate the placement of a noncutting seton instead of fistulotomy in patients with simple fistulae and active Crohn's proctitis. A noncutting seton is a drain that is placed through the fistula tract by the external opening of the fistula. It then is passed into the rectum by the internal opening of the fistula and finally extends out the anal canal, where both ends are loosely tied. Setons function by allowing fistulous tracts to drain, with the goal of

Table 2
Controlled trials for treatment of fistulizing Crohn's disease with immunomodulators and biologic agents

Author, year	N	Drug, dose	Rx time	Response drug (%)	Response placebo (%)	*P* value
Immunomodulators						
Azathioprine/6-MP						
Willoughby et al, 1971 [75]	3	Azathioprine, 2 mg/kg/d	24 wk	0/2 (0)	0/1 (0)	NR
Rhodes et al, 1971 [76]	6	Azathioprine, 2 mg/kg/d	2 mo	2/4 (50)	0/2 (0)	NR
Klein et al, 1974 [77]	10	Azathioprine, 3 mg/kg/d	4 mo	4/5 (80)	2/5 (40)	NR
Rosenberg et al, 1975 [78]	5	Azathioprine, 2 mg/kg/d	26 wk	0/4 (0)	1/1 (100)	NR
Present et al, 1980 [79]	46	6-MP, 1.5 mg/kg/d	1 y	16/29 (55)	4/17 (24)	NR
TOTAL	70			22/44 (50)	7/26 (27)	
Tacrolimus						
Sandborn et al, 2003 [108]	48	Tacrolimus, 0.2 mg/kg/d	10 wk	9/21 (43)	2/25 (8)	.004
Biologic agents						
Infliximab						
Present et al, 1999 [113]	94	Infliximab, 5 mg/kg	14 wk	21/31 (68)	8/31 (26)	.002
		Infliximab, 10 mg/kg		18/32 (56)		.02
Sands et al, 2004 [114]	195	Infliximab, 5 mg/kg	54 wk	42/91 (46)	23/98 (23)	.001
				Time to loss of response $\geq$40 wk	Time to loss of response = 14 wk	<.001
TOTAL	289			81/154 (53)	31/129 (24)	
CDP571						
Sandborn et al, 2001 [135]	37	CDP571, 10 or 20 mg/kg	24 wk	12/24 (50)	2/13 (15)	.074

Abbreviations: 6-MP, 6-mercaptopurine; N, number of patients; NR, not reported; Rx, treatment.

Table 3
Uncontrolled trials for treatment of fistulizing Crohn's disease with immunomodulators and biologic agents

Author, year	N	Drug, dose	Initial response (%)	Sustained response (%)
Immunomodulators				
Methotrexate				
Mahadevan et al, 2003 [89]	16	Methotrexate, 25 mg/wk im	9/16 (56)	3/16 (19)
Cyclosporin A				
Fukushima et al, 1989 [92]	1	Cyclosporin A, 8 mg/kg/d po	1/1 (100)	1/1 (100)
Lichtiger, 1990 [93]	10	Cyclosporin A, 4 mg/kg/d iv	6/10 (60)	NR
Markowitz et al, 1990 [94]	1	Cyclosporin A, 4 mg/kg/d iv	0/1 (0)	0/1 (0)
Hanauer and Smith, 1993 [95]	5	Cyclosporin A, 4 mg/kg/d iv	5/5 (100)	2/5 (40)
Present and Lichtiger, 1994 [96]	16	Cyclosporin A, 4 mg/kg/d iv	14/16 (88)	9/16 (56)
Abreu-Martin et al, 1996 [97]	2	Cyclosporin A, 2.5 mg/kg/d iv	2/2 (100)	1/2 (50)
O'Neill et al, 1997 [98]	8	Cyclosporin A, 4 mg/kg/d iv	7/8 (88)	0/8 (0)
Hinterleitner et al, 1997 [99]	7	Cyclosporin A, 5 mg/kg/d iv	9/9 (100)	4/9 (44)
Egan et al, 1998 [100]	9	Cyclosporin A, 4 mg/kg/d iv	7/9 (78)	2/8 (25)
Gurudu et al, 1999 [101]	3	Cyclosporin A, 4 mg/kg/d iv	2/3 (67)	NR
TOTAL	64		53/64 (83)	19/50 (38)
Biologic agents				
Adalimumab				
Sandborn et al, 2004 [133]	9	Adalimumab, 80/40 mg qow	5/9 (56)	NR
Thalidomide				
Ehrenpreis et al, 1999 [136]	13	Thalidomide, 200 or 300 mg/d	9/13 (69)	NR
Vasiliauskas et al, 1999 [137]	6	Thalidomide, 50 or 100 mg/d	1/6 (17)	NR
TOTAL	19		10/19 (53)	NR

Abbreviations: im, intramuscular; iv, intravenous; N, number of patients; NR, not reported; po, oral; qow, every other week.

preventing abscess formation. Unfortunately, the rate of fistula relapse following removal of a seton is high, with up to a 63% recurrence rate reported in surgical case series [167,171,172,176,177]. The placement of a seton does not improve the rectal inflammation, however, and medical therapy with topical 5-aminosalicylic acid agents or corticosteroids is needed. In patients whose

proctitis does not improve with these medications, infliximab should be considered early, ideally before the fistula becomes complex [5].

Complex perianal Crohn's fistulae have considerably lower rates of healing than simple fistulae. Management of complex fistulae almost always requires combination medical and surgical therapy. Complex fistulae are frequently associated with the development of perianal abscesses, rectovaginal fistulae, or anorectal strictures. Management of these fistulae often includes drainage of abscesses, repair of rectovaginal fistulae, and dilation of anorectal strictures. Noncutting setons should be placed to facilitate continued drainage of infectious material and to prevent any abscesses from recurring. In patients without abscesses, setons are still important to allow fistula drainage and prevent de novo abscess formation. It is often necessary to leave setons in place long-term, because relapse rates are high on seton removal. At this point, aggressive medical therapy becomes important to assist in the fistula healing process. Current recommended medical treatment options include antibiotics; immunomodulators (6-mercaptopurine, azathioprine, or methotrexate); and infliximab. Again, it is unclear at the present time which strategy is most efficacious, because of lack of controlled data and lack of comparison data. Antibiotics are necessary in patients with abscess formation, and a course of antibiotics is often given to patients who do not have an abscess. Infliximab has become increasingly popular in the treatment of complex fistulae and is often combined with an immunomodulator, because immunomodulators themselves have efficacy in this setting and also help to decrease immunogenicity to infliximab.

SUMMARY

The treatment of fistulizing CD has evolved greatly in the last 15 years, largely caused by improvements in medical therapy. Tables 2 and 3 summarize all published controlled and uncontrolled trials of immunomodulator and biologic therapy for the treatment of Crohn's fistulae. The advent of immunomodulators and anti–TNF-α agents has transformed the treatment of Crohn's fistulae from almost exclusively surgical to placing a much larger emphasis on medical therapy, either as initial therapy alone, with surgery reserved for refractory cases, or in combination with surgery from the start. For this reason, surgeons and gastroenterologists must work in concert to provide the best care for each patient. Proper fistula management also relies heavily on accurate diagnosis, especially defining the anatomy of the fistula, ascertaining whether abscess formation is present, and determining the location and extent of intestinal inflammation.

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Infliximab in Ulcerative Colitis

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Until recently development of new medical therapies for the treatment of patients who have ulcerative colitis (UC) has been somewhat stagnant. The standard treatment pyramid for active UC has been a step-up approach. Initially, 5-aminosalicylates are used for the treatment of mild-to-moderate UC. If 5-aminosalicylates fail, corticosteroids are used as bridge either to higher doses of 5-aminosalicylates or to immunomodulators (6-mercaptopurine or azathioprine). When UC is severe, intravenous corticosteroid or cyclosporine is used as a bridge to oral immunomodulator therapy (6-mercaptopurine or azathioprine). Surgery also is contemplated for appropriate patients in whom medical therapy fails or has unacceptable potential adverse events. Infliximab, a chimeric monoclonal antibody directed against tumor necrosis factor α (TNF-α), was tested initially in patients who had Crohn's disease (CD) and currently is a standard agent in the medical armamentarium for treatment of these patients. In 2005, results of two prospective, randomized, placebo-controlled clinical trials demonstrated that infliximab also is extremely efficacious for treatment of UC. This article provides information about the evolution of anti-TNF therapy for the treatment of UC.

TUMOR NECROSIS FACTOR-α

TNF-α is a cytokine involved in immune regulation leading to enhanced leukocyte cell proliferation [1,2]. The inflammatory cascade triggered by stimuli such as lipopolysaccharide and other bacterial antigens involves release of several inflammatory cytokines including TNF-α as well as other proinflammatory cytokines such as interleukin (IL)-4 and IL-12, primarily by activated macrophages. T lymphocytes, monocytes, natural killer cells, and mucosal mast cells also have been shown to produce TNF-α. TNF-α is translated into a 26-kd protein precursor and circulates as 17-kd nonglycosylated protein. TNF-α receptors, type I 55-kd, and type II 75-kd TNF receptors are expressed on most cells of the human body [1]. Both TNF-α and lymphotoxin-α, produced by lymphocytes and natural killer cells, bind to these receptors [3]. In animal

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knockout models, the absence of TNF-α and lymphotoxin-α leads to absent lymph nodes and decreased lipopolysaccharide responses. Absent 55-kd receptor leads to decreased lipopolysaccharide responses and failure to contain infections such as *Listeria* and *Mycobacterium* [4,5]. Absence of 75-kd receptor leads to decreased lymphocyte proliferation, dermal response to TNF, and TNF-induced lethality [6,7]. TNF-α promotes expression of several downstream proinflammatory signaling molecules, IL-6, IL-8, IL-1, adhesion molecules (intercellular adhesions molecules and vascular cell adhesion molecules), and nitric oxide synthase, ultimately leading to recruitment of circulating inflammatory cells, primarily neutrophils, to local sites of inflammatory initiation. Many of the downstream cytokines triggered by TNF-α promote neutrophil adhesion to endothelial cells (IL-8, intercellular adhesions molecules, and vascular cell adhesion molecules) [1]. TNF-α directly and indirectly also induces platelet-activating factor, the coagulation cascade, and fibrinolysis. TNF-α also mediates granuloma formation by inducing production of chemokine monocytes chemoattractant protein-1, leading to recruitment of monocytes [6,8,9].

TUMOR NECROSIS FACTOR-α AND INFLAMMATORY BOWEL DISEASE

Significant evidence suggests that the mechanism leading to inflammatory bowel disease is an aberrant immune response. There are data suggesting a lack of immune tolerance to commensal enteric bacteria. Antigen-presenting cells such as dendritic cells are stimulated by enteric antigens such as bacteria, and the antigen-presenting cells trigger activation of T cells. Antigen-presenting cells differentiate T cells into effector or regulatory cells.

In inflammatory bowel disease the immune response persists with lack of tolerance to nonpathogenic enteric bacteria. Data in CD suggest a resistance to effector T-cell apoptosis [10].

T cells differentiate into cells that are characterized by their cytokine production: T-helper 1 (Th1), T-helper 2 (Th2), and regulatory T cells. Th1 cells produce interferon γ, TNF-α, lymphotoxin, IL-2, IL-12, and IL-18 and yield a cell-mediated immunity response [11,12]. Th2 cells result in IL-4, IL-5, IL-10, and IL-13 production [12]. Th1 response is reduced by suppressor cytokines such as transforming growth factor β and IL-10 produced by regulatory T cells [13]. Th2 response also seems to be suppressed by transforming growth factor β but at higher levels than required than for suppression of a Th1 response [13].

The immune response in UC initially was believed to be characterized by domination of Th2 lymphocytes in colonic mucosa [14]. The UC immune response, however, is characterized by increased secretion of IL-5, but not IL-4 or interferon-γ, by lamina propria lymphocytes, and by a lack of increase of IL-12 [14–16]. The diminished IL-4 response is associated with activating natural killer cells and IL-13 secretion [17]. Additionally, studies have shown increased levels of TNF-α in the colonic mucosa, serum, and stool of patients who have UC, and the degree of elevation correlates with disease activity

[16,18–23]. Another study found elevated levels of IL-6, IL-8, TNF-α, TNF-α receptors, p55, and p75 that correlated with the degree of inflammation [24,25]. TNF-α secreting cells are increased in the mucosa and submucosa of inflamed intestine in both CD and UC, but TNF-α levels are higher in patients who have CD [26–28]. In a pediatric study, TNF-α–secreting cells were measured using ELISA from biopsies of normal colon and biopsies of colon from patients who had inflammatory bowel disease. All nine biopsies from patients who had CD had elevated TNF-α–secreting cells, compared with four of eight of patients who had UC, two of three patients who had indeterminate colitis, and 6 of 12 subjects who had normal colons [29]. Increased expression of IL-8, TNF-α, and interferon-γ mRNA has been detected even in inactive UC, suggesting that these cytokines play a pivotal role in relapse of UC [30]. It was suggested that TNF-α is one possible mediator of the increased IL-8 synthesis in active UC [31,32]. IL-8 is thought to mediate local mucosal recruitment and activation of neutrophils in UC [32]. It also has been suggested that in UC TNF-α is involved in cell injury in the colonic epithelium by increasing antibody-dependent cellular cytotoxicity activity [33]. These findings prompted the evaluation of anti–TNF-α treatment in UC.

TNF-α may induce resistance to apoptosis in some cells. In T cells, specifically, TNF-α induces transcription factor nuclear factor κB, leading to resistance to apoptosis [34]. After the development of anti-TNF therapies it was realized that anti-TNF therapies lead to T-cell apoptosis [34,35].

ANTI–TUMOR NECROSIS FACTOR THERAPY AND INFLAMMATORY BOWEL DISEASE

Animal Data

In murine models of colitis, there are several methods of inducing colitis that may not resemble the mechanism by which humans develop colitis. In a murine model of inflammatory bowel disease that was induced in CB-17 SCID mice by transfer of the CD45RBhi subpopulation of CD4-positive T cells from normal BALB/c mice, anti-TNF antibodies reduced the incidence of severe disease, although no effect was seen in the first 3 to 4 weeks of administration of antibody [36]. In another murine model of colitis, the use of oral avian anti-TNF antibodies was compared with sulfasalazine, dexamethasone, and placebo for the treatment of colitis; oral anti-TNF antibodies seemed to be most effective [37]. In a murine model of colitis induced with dextran sulfate sodium, TNF was not detectable in colonic tissue extracts or in plasma. Anti-TNF antibody was infused and failed to reduce the severity of colitis induced by dextran sulfate sodium [38]. In a more recent study evaluating cytokine response in dextran sulfate sodium–induced murine colitis, anti-TNF therapy was found to aggravate acute colitis, whereas chronic colitis improved with anti-TNF therapy [39]. In another murine model of colitis using intracolonic instillation of the hapten trinitrobenzenesulphonic acid in ethanol, anti-TNF therapy did not play a significant role in improvement of colitis [40]. This study demonstrated the importance of using colitis models that more

closely resemble human inflammatory bowel disease to understand pathophysiologic mechanisms.

The Cottontop tamarin is a primate that in captivity spontaneously develops an inflammatory bowel disease that is similar to UC in humans. CDP571, an engineered human monoclonal antibody to TNF-α, was tested in Cottontop tamarins that had inflammatory bowel disease. In a study by Watkins and colleagues [41], six Cottontop tamarins that had UC were treated with CDP571, and all showed improvement clinically and by rectal biopsy [41]. Four of the six Cottontop tamarins required no additional therapy 18 months after receiving a last dose of CDP571 [41].

Infliximab

Infliximab is a 149,100-d chimeric monoclonal antibody directed against TNF-α (Fig. 1). The variable domain is murine derived and is linked to a human IgG1 constant region [42–44]. Infliximab binds to both soluble and transmembrane TNF-α.

PHARMACOKINETICS

Data from clinical studies using single intravenous infusions of infliximab (5, 10, and 20 mg/kg) showed a direct relationship between the dose administered and the maximum serum concentration [45]. Its route of metabolism and excretion is unknown, and the rate of clearance is dose independent. Infliximab has a slow rate of clearance, 9.8 mL/h, and high affinity for TNF-α ($K_a = 10^{10}\ m^{-1}$) [45]. A single 5 mg/kg dose of infliximab had a serum half-life of 9.5 days, remaining primarily in the vascular compartment (Vdss = 3 L) [45,46]. Levels decline in an exponential fashion and usually are undetectable at week 12 [45].

MECHANISM OF ACTION

The mechanism of action of infliximab is not clear but probably involves interference with the functions of TNF-α. The variable region of this antibody

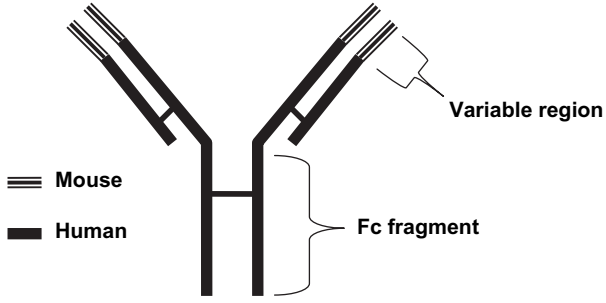

Fig. 1. Infliximab.

binds to both soluble and transmembrane TNF-α with high affinity and specificity. The constant region mediates its effector functions including antibody-dependent cellular toxicity, complement fixation, antibody clearance, and apoptosis of T lymphocytes [42,47–49].

THERAPEUTIC USE

The Food and Drug Administration (FDA) has approved the use of infliximab for several indications. The initial indication was for reducing the signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients who have moderately to severely active rheumatoid arthritis and who have had an inadequate response to methotrexate [50,51]. Soon after its approval for rheumatoid arthritis, infliximab was approved by the FDA for reducing the signs and symptoms and inducing and maintaining clinical remission in patients who have moderately to severely active CD and who have had an inadequate response to conventional therapy [50,52]. In addition, infliximab is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients who have fistulizing CD [50,51,53]. Infliximab also is FDA approved for reducing signs and symptoms in patients who have active ankylosing spondylitis or psoriatic arthritis [50,53]. The most recent FDA-approved indication for infliximab is for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients who have moderately to severely active UC who have had an inadequate response to conventional agents [50,53].

INFLIXIMAB FOR TREATMENT OF ULCERATIVE COLITIS

There have been six randomized, double-blind, controlled trials of infliximab for the treatment of UC, although there is heterogeneity in the severity of UC in the trials as well as in the primary end points of the studies. The early studies indicated that infliximab had promise for the treatment of active UC, and the most recent studies confirm its superiority over placebo in clinical response, clinical remission, mucosal healing, reduction of dose, and discontinuation of corticosteroid (Table 1) [54–58].

Current therapeutic management for severe UC consists of in-patient administration of intravenous corticosteroids. If this treatment fails to control the disease after 7 to 10 days, the options are intravenous cyclosporine or proctocolectomy [59,60]. Cyclosporine has several side effects, such as hypertension, renal insufficiency, and opportunistic infections, and cyclosporine requires vigilant dose monitoring [54,56,58]. In an early pilot randomized study by Sands and colleagues [56], 8 of 11 patients who had severe UC (Truelove and Witts score >10) refractory to steroids received a single infusion of 5 mg/kg (n = 3), 10 mg/kg (n = 3), or 20 mg/kg (n = 2) infliximab; three patients received placebo. The primary end point was treatment failure after 2 weeks. Formal statistics were not performed because of the small size of

Table 1
Randomized, controlled trials of infliximab for ulcerative colitis

Author (year)	Number of patients	Dose (follow-up)	Treatment	Response[a] n (%)	*P*-value
Sands, et al (2001)	11	Single (2 weeks)	Infliximab: 8 patients Placebo: 3 patients	4 (50) 0 (0)	-
Probert, et al (2003)	43	Multiple (6 weeks)	Infliximab: 23 patients Placebo: 20 patients	9 (39) 6 (30)	.76
Ochsenkuhn, et al (2004)	13	Multiple (13 weeks)	Infliximab: 6 patients Prednisolone: 7 patients	8 (83.3) 6 (85.7)	.7
Järnerot, et al (2005)	45	Single (3 months)	Infliximab: 24 patients Placebo: 21 patients	17 (70.8) 7 (33.3)	.017
Rutgeerts et al, ACT 1 (2005)	364	Multiple (54 weeks)	Infliximab: 5mg/kg: 121 patients 10mg/kg: 122 patients Placebo: 121 patients	55 (45.5) 54 (44.3)[b] 24 (19.8)	<.001
Sandborn et al, ACT 2 (2005)	364	Multiple (30 weeks)	Infliximab: 5mg/kg: 121 patients 10mg/kg: 120 patients Placebo: 123 patients	57 (47.1) 72 (60) 32 (26)	<.001

Abbreviation: ACT, Active Ulcerative Colitis Trial.
[a]Response may mean avoidance of colectomy or decrease in disease activity score depending on the particular study's primary outcome.
[b]$P = .002$ compared with placebo.

the trial. All patients who received placebo but only four of the eight patients (50%) who received infliximab required colectomy. Clinical response correlated with decreases in erythrocyte sedimentation rate and serum levels of C-reactive protein and circulating IL-6. The decrease in modified Truelove and Witts criteria was noted in five of the eight patients who received infliximab, four of whom avoided colectomy. In a study by Jarnerot and colleagues [54], forty-five patients hospitalized for severe UC who had received intravenous betamethasone (4 mg) twice daily and continued to have an elevated disease activity index by day 4 (Seo index ≥ 8) were randomly assigned to intravenous infliximab (5 mg/kg) or placebo. Patients who responded to therapy were switched to oral prednisone (40 mg/d) with a dose reduction of 5 mg/wk. Patients also were given mesalamine for maintenance, and azathioprine (1.5–2 mg/kg) could be added for maintenance based on the discretion of the physician. The primary end point of the study was colectomy or death 3 months after randomization. Twenty-nine percent of infliximab users had colectomy by 3 months after randomization, compared with 67% of placebo recipients ($P = .017$). All colectomies occurred within 30 days of randomization, with a median time to surgery of 8 days (range, 2–22 days) in the infliximab group and 4 days (range, 1–13 days) in the placebo group. Eight patients (five in the infliximab arm and three in the placebo arm) were taking azathioprine at the time of inclusion of the study. One of five patients taking azathioprine in the infliximab

arm had a colectomy, as compared with two of three patients assigned to placebo. There were no deaths in the study.

In an early randomized study of infliximab for moderate UC, 43 patients who did not respond to oral corticosteroids were randomly assigned to infliximab (two doses: week 0 and week 2) or placebo [58]. Patients were evaluated at week 6 for remission based on a UC symptom index score of 2 or lower and a Baron score of 0 by sigmoidoscopy. At week 6, 39% of patients who received infliximab were in remission, compared with 30% of placebo recipients ($P < .76$). At the start of the study the prednisone dose was not standardized in the treatment arms; the mean prednisone dose was 32 mg/d in the treatment arum and 28 mg/d in the placebo arm. Patients who also were receiving azathioprine at the start of the trial were more likely to achieve remission if they were in the infliximab arm (four of six, 67%) than in the placebo arm (two of six, 33%), but, given the small numbers in this subgroup analysis, the trend was not statistically significant.

Another small, randomized, controlled trial by Ochsenkühn and colleagues [57] assessed the efficacy of infliximab for treatment of moderate active UC in patients who were not already receiving corticosteroids and azathioprine. Six of 13 patients were randomly assigned to one dose of infliximab (5 mg/kg), and 7 were assigned prednisone (1.5 mg/kg/d). Clinical response (a decrease in Truelove and Witts score of at least 5 points from baseline and a total score <10) was assessed at weeks 3 and 13. Both groups had a response to therapy (five of six in the infliximab group and six of seven in the prednisone group) [57].

The largest and longest-duration randomized, controlled trials to date assessing the efficacy of infliximab for treatment of UC are the Active Ulcerative Colitis Trials (ACT 1 and ACT 2) [55]. These trials assessed the efficacy of infliximab for treatment of moderate-to-severe UC [55]. In the ACT 1 trial 364 patients who had not responded to corticosteroids alone or in combination with azathioprine or 6-mercaptopurine were randomly assigned to receive placebo, infliximab (5 mg/kg), or infliximab (10 mg/kg). Patients received treatment at weeks 0, 2, and 6 and then every 8 weeks until week 46, the end of the study. The primary end point was clinical response at week 8 with response at weeks 30 and 54 a secondary end point. As a secondary end point patients also were assessed for clinical remission and mucosal healing at weeks 8, 30, and 54. Clinical remission was defined as a Mayo score of 2 points or less and a Mayo subscore increase no greater than 1. Clinical response was defined as a decrease in the Mayo score of at least 3 points, a decrease by at least 30% with decrease in the rectal bleeding score by more than 1 point, or a score of 0 or 1.

Of the patients who had UC who participated in the ACT 1, 61% were taking corticosteroids, and approximately 49% were taking azathioprine or 6-mercaptopurine upon entry into the trial [55]. There was no significant difference in the use of corticosteroids or immunosuppressants among the three groups. Of the corticosteroid users approximately one third was refractory to corticosteroids. Half the patients participating had left-sided disease, and half the patients had extensive disease. The only baseline characteristic that differed

among the three groups was duration of disease: patients receiving infliximab (10 mg/kg) had the longest duration of disease, 8.4 (SD ± 8.1) years, compared with 6.2 (SD ± 5.9) years in the placebo arm and 5.9 (SD ± 5.4) years in patients receiving 5 mg/kg of infliximab ($P < .03$). For the primary end point, clinical response rates at week 8 were 37.2%, 69.4%, and 61.5% for patients receiving placebo, infliximab (5 mg/kg), and infliximab (10 mg/kg), respectively ($P < .001$ for both infliximab arms) (Table 2). Clinical remission at week 8 occurred in 14.9% of those receiving placebo, 38.8% of those receiving infliximab (5 mg/kg) ($P < .001$), and 32% of those receiving infliximab (10 mg/kg) ($P = .002$) (see Table 2). At week 8 mucosal healing corresponded to the rates of clinical response: 33.9% of patients receiving placebo, 62% of patients

Table 2
Results from the Active Ulcerative Colitis Trials

	ACT 1			ACT 2		
	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Week 8						
Response (%)	37.2	69.4[a]	61.5[a]	29.3	64.5[a]	69.2[a]
Remission (%)	14.9	38.8[a]	32[b]	5.7	33.9[a]	27.5[a]
Mucosal healing (%)	33.9	62[a]	59[a]	30.9	60.3[a]	61.7[a]
Week 30						
Response (%)	29.8	52.1[a]	50.8[a]	26	47.1[a]	60[a]
Remission (%)	15.7	33.9[c]	36.9[a]	10.6	25.6[d]	35.8[a]
Remission and discontinued corticosteroids (%)	10.1	24.3[f]	19.2[g]	3.3	18.3[h]	27.3[a]
Mucosal healing (%)	24.8	50.4[a]	49.2[a]	30.1	46.3[e]	56.7[a]
Week 52						
Response (%)	19.8	45.5[a]	44.3[b]	-	-	-
Remission (%)	16.5	34.7[c]	34.4[c]	-	-	-
Remission and discontinued corticosteroids (%)	8.9	25.7[i]	16.4[i]	-	-	-
Mucosal healing (%)	18.2	45.5[a]	46.7[a]			

Abbreviation: ACT, Active Ulcerative Colitis Trial.
[a] $P < .001$.
[b] $P = .002$.
[c] $P = .001$.
[d] $P = .003$.
[e] $P = .009$.
[f] $P = .030$.
[g] $P = .125$.
[h] $P = .01$.
[i] $P = .006$.
[i] $P = .149$.

receiving the lower dose of infliximab, and 59% of patients receiving the higher dose of infliximab ($P < .001$ for both infliximab arms). At week 54 there was a significant difference in clinical remission between the placebo arm and the infliximab arms ($P < .001$), with 16.5% of those receiving placebo, 34.7% of those receiving infliximab (5 mg/kg), and 34.4% of those receiving infliximab (10 mg/k) in remission. Once again at week 54 the rates of clinical response correlated with mucosal healing rates, with a significant difference in rates between the placebo arm (approximately 20%) and the infliximab arms (approximately 50%) ($P < .001$). At week 54, 8.9% of patients receiving placebo were in remission and discontinued corticosteroids, compared with 25.7% receiving the lower dose of infliximab (5 mg/kg) ($P = .006$) and 16.4% receiving the higher dose (10 mg/kg) ($P = .149$). The group with the greatest reduction in corticosteroid dose at week 54 compared with baseline was in the arm receiving the lower dose of infliximab (5 mg/kg), with the median dose of 20 mg at baseline decreasing to 5 mg at week 54. A reduction in corticosteroid use also was observed in the group receiving 10 mg/kg infliximab, although the reduction was not as great as seen in the 5 mg/kg arm: the baseline median corticosteroid dose of 20 mg decreased to 10 mg at week 54. There was no change from the median corticosteroid dose at baseline to the median dose at week 54 in the placebo arm. Overall, infliximab seems to be effective in patients who have not responded to corticosteroids or immunosuppressants (azathioprine or 6-mercaptopurine), although a dose response was not observed, with no additional benefit seen at 10 mg/kg. Longer duration of disease in the group receiving the higher dose of infliximab may account for lack of additional benefit observed.

ACT 2 assessed the efficacy of infliximab in patients who had moderate-to-severe UC that did not respond to 5-aminosalicylates or to corticosteroids alone or in combination with azathioprine or 6-mercaptopurine. The trial design was similar to ACT 1 with three randomly assigned arms: infliximab (5 mg/kg) or infliximab (10 mg/kg). Patients received an induction regimen (weeks 0, 2, and 6) and maintenance infliximab (every 3 weeks) until week 22 and were followed until week 30. The primary end point was the same as in ACT 1: clinical response at week 8. Secondary end points also were the same: clinical remission and mucosal healing at weeks 8 and 30 and clinical remission with discontinuation of corticosteroids. The only baseline characteristic differing among the three arms was race ($P = .03$), although more than 90% of patients in each arm were of the white race. Approximately 50% of patients in the ACT 2 trial were taking corticosteroids; one third was refractory to corticosteroids. One third of patients using corticosteroids upon entry in to the trial was taking more than 20 mg/d. Forty percent of patients were using azathioprine or 6-mercaptopurine upon entry, and approximately 75% were using 5-aminosalicylates, although the percentage of patients using only 5-aminosalicylates upon entry was not provided. At week 8, the primary end point of clinical response, there was a significant difference between the infliximab-treated patients and the placebo arm ($P < .001$): 64.5%

of patients receiving infliximab (5 mg/kg), 69.2% of patients receiving infliximab (10 mg/kg), and 29.3% of placebo-treated patients had a clinical response. Mucosal healing rates and remission were similar to results in ACT 1, with infliximab superior to placebo and no significant advantage seen with the higher 10 mg/kg dose of infliximab compared with the 5-mg/kg dose (see Table 2). By week 30 18.3% of patients in the infliximab 5-mg/kg arm and 27.3% of patients in the infliximab 10-mg/kg arm, as compared with 3.3% of placebo patients, were in remission and discontinued corticosteroids (see Table 2).

TOXICITY OF INFLIXIMAB IN THE ULCERATIVE COLITIS TRIALS

Infections

In the trials of infliximab for CD therapy, infectious complications occurred in one third of patients involved in the trial, but the patients receiving infliximab did not have higher rates of infection than the control groups [55]. Additionally, serious infections requiring antimicrobial therapy occurred in less than 10% of patients, and there was no significant difference between active-treatment and control arms. The rheumatoid arthritis trials revealed similar risks for infection, except that upper respiratory infections (34% versus 22%), sinusitis (17% versus 6%), and pharyngitis (11% versus 6%) occurred more frequently in the infliximab recipients than in controls [61]. In the largest and longest-duration trials of infliximab for treatment of UC, ACT 1 and ACT 2, infectious complications were highest in the ACT 1 trial; this finding may be biased by the longer follow-up in ACT 1. Infections over the course of the 1-year ACT trial occurred in 38.8% of patients who received placebo, 43.8% of patients who received infliximab (5 mg/kg), and 49.2% of patients who received infliximab (10 mg/kg) ($P = .18$). There was no significant difference in serious infections. There were higher rates of serious infections requiring antibiotics in the infliximab arms than the placebo arm: 32.2% of patients who received infliximab (5 mg/kg), 35.2% of patients who received infliximab (10 mg/kg), and 20.7% in the placebo group ($P = .01$). In ACT 2 infections occurred less frequently, and there was no significant difference in infection rates among the three arms of the trial. Infections reported slightly more frequently in the infliximab arms of the trial included pneumonia, *Herpes zoster*, Histoplasmosis (one case was fatal), and tuberculosis (one case was fatal).

Although the clinical trials showed few differences in risk of infection between the patients exposed to infliximab and those receiving placebo, postmarketing studies have provided additional information, as is usually the case for rare adverse events. Postmarketing studies have revealed concern for reactivation of *Mycobacterium tuberculosis* by infliximab: data from the FDA Adverse Event Reporting System in 2001 reported 70 cases of tuberculosis in 147,000 patients exposed to infliximab (0.047%) [62]. In 2003 a review by Rutgeerts [44] found that 350 of 400,000 patients (0.08%) who received infliximab developed active tuberculosis, and the cumulative mortality was 9%. By 2005 there were 709 reported cases of tuberculosis and 62 deaths attributable to

tuberculosis in infliximab users (the number of infliximab users was not given) [63]. The increased risk for reactivation of tuberculosis also has been demonstrated in animal models showing TNF-α to be an important mediator in granuloma formation and blockade of TNF-α by antibodies leading to activation of latent tuberculosis. Therefore, tuberculosis screening by chest radiographs and tuberculin skin test is mandatory in all patients before initiating infliximab therapy.

Neurologic Diseases

In the infliximab arms of the ACT trials there were more frequent neurologic events (two cases of optic neuritis and one case of multifocal motor neuropathy) than in the placebo arm. There have been prior reports of neurologic sequelae in patients receiving infliximab; induction of demyelination os believed to be the underlying mechanism. Mohan and colleagues [64] reported data from the FDA Adverse Events Reporting System revealing 19 reports suggestive of demyelination associated with anti–TNF-α therapy for inflammatory arthritis. In the FDA-reported cases paresthesias and visual disturbances were most common, but confusion, gait disturbance, apraxia, facial palsy, and Guillain-Barré syndrome also occurred. All neurologic events were associated temporally with anti–TNF-α therapy with partial or complete resolution on discontinuation. One patient developed a positive rechallenge phenomenon (reappearance of symptoms upon re-exposure to the agent), but another individual tolerated reinstitution of anti–TNF-α therapy at a lower dose without further neurologic sequelae [64]. A recent study by Gupta and colleagues [65] suggests that patients who have inflammatory bowel disease may be at underlying risk for demyelinating diseases independent of anti-TNF therapy.

Antibodies to Infliximab

Infusion reactions to infliximab are categorized as acute reactions (occurring < 24 hours after the infusion) or delayed reactions (occurring 1–14 days after the infusion) [66]. Acute reactions to infliximab predominantly are non–IgE-mediated reactions, whereas delayed infusion reactions are characterized by the presence of antibodies to infliximab and probably represent several adverse reactions: a type III hypersensitivity response (serum sickness), a serum sickness–like reaction, lupuslike reactions, viral-type syndrome, flare of inflammatory bowel disease, and nonspecific reactions (arthralgia, myalgias, fever, urticarial rash, and malaise) [66].

Before the UC trials, randomized, controlled studies of infliximab reported that 11% to 17% of patients developed antibodies to infliximab during treatment with infliximab. Patients who had antibodies to infliximab had a twofold greater risk for infusion reaction [52,67–69]. Higher levels of antibodies to infliximab and episodic therapy increase the risk for infusion reactions. Additionally, the presence of antibodies to infliximab is associated with decreased infliximab concentrations at 4 weeks and a shorter duration of response [70].

In the ACT trials no significant difference in antibodies to infliximab were observed based on the dose of infliximab (ACT 1: 7.8% for 5 mg/kg infliximab; 4.4% for 10 mg/kg infliximab. ACT 2: 9.5% for 5 mg/kg infliximab; 3.2% for 10 mg/kg infliximab) [55]. There was a low rate of acute and delayed infusion reactions in the ACT trials, although acute infusion reactions (8.1%–12.3%) were more common than delayed reactions (0–1.7%) [55]. There was no difference in infusion reactions in infliximab recipients and placebo recipients. Approximately one third of infliximab recipients in both the ACT 1 and ACT 2 trials developed antinuclear antibodies, compared with 7.3% to 7.4% of those who received placebo ($P < .001$). Anti–double-stranded DNA antibodies also occurred at higher rate in the infliximab arms of the trial than in the placebo arm. One patient exposed to infliximab developed a lupuslike reaction [55].

Malignancy

As of February 2003, postmarketing surveillance has documented 71 cases of lymphoma among 365,000 patients treated with infliximab (45 of whom had rheumatoid arthritis, and 20 of whom had CD) [44]. Cases of an aggressive hepatosplenic T-cell lymphoma that have led to several fatalities have been reported in adolescents and young adults. All patients were taking both infliximab and 6-mercaptopurine or azathioprine [53].

Patients who have rheumatoid arthritis have a higher baseline risk for lymphoma, but this increased risk has not been shown in inflammatory bowel disease independent of immunosuppressants [69,71,72]. There were no reported cases of lymphoma in the ACT trials.

Nine cases of nonlymphomatous malignancies have been reported in the 1283 patients from the three major clinical trials of infliximab in CD and rheumatoid arthritis, an incidence of 0.7% [52,67–69]. In a retrospective cohort study of 500 patients who had CD treated with infliximab, there were seven cases of malignancy (1.4%) [73]. There was no apparent association between the dose of infliximab or time from treatment and development of malignancy [73]. The therapy, resource, evaluation, and assessment tool registry reports a similar incidence of malignancies in patients who have CD treated and not treated with infliximab [74]. In the ACT 1 trial there were two cases of malignancy: prostate cancer in one patient who had an elevated prostate-specific antigen level before the trial, and basal cell cancer in another patient; both cases occurred in patients receiving infliximab [55]. One patient receiving infliximab (5 mg/kg) developed colonic dysplasia [55]. In the ACT 2 trial, one patient in the 5 mg/kg infliximab arm developed rectal adenocarcinoma, and one patient who received placebo developed basal cell carcinoma [55].

Contraindications

By the prescribing guidelines, infliximab at doses greater than 5 mg/kg is contraindicated in patients who have moderate-to-severe (New York Heart Association class III/IV) congestive heart failure. Infliximab should not be given to patients who have a known hypersensitivity to a murine protein or component of the product [53].

WHEN TO USE INFLIXIMAB FOR THE TREATMENT ULCERATIVE COLITIS

Currently, the medications used to treat UC include 5-aminosalicylates, corticosteroids, 6-mercaptopurine, azathioprine, and, for severe disease, cyclosporine. Based on the published clinical trials, the use of infliximab has been demonstrated to be beneficial in patients who have UC who have not responded to of 5-aminosalicylates, who have not responded to or are intolerant of 6-mercaptopurine or azathioprine, who have corticosteroid-dependent disease, and as rescue in severe disease as an alternative to cyclosporine after intravenous corticosteroids. There certainly are other indications not put to the test in clinical trials, including patients who are not willing to use corticosteroids because of their potential risk. The use of infliximab for the indications that have been assessed in clinical trials and for indications not formally tested in clinical trials that may occur in clinical practice (eg, individuals who are not willing or able to taken the risk of using other medications or who have extra-intestinal manifestations that parallel disease activity) should be evaluated on an individual basis, assessing the risk–benefit ratio compared with other available medical therapeutic options.

SUMMARY

Infliximab is effective for treatment of moderate-to-severe UC and is recommended for patients who have had an inadequate response to medical therapy or who are intolerant of or do not desire to take the potential risk of using specific agents including immunomodulators (cyclosporine A, azathioprine, or 6-mercaptopurine), corticosteroids, and, potentially, mesalamine. Future trials are needed to assess the efficacy of infliximab with immunomodulators to see if additional benefit is achieved so that the risk–benefit ratio is positive. Based on the favorable efficacy of infliximab for UC therapy, the ground work has been established for evaluating infliximab and addressing some of the many unanswered questions and also for assessing other anti-TNF agents and streamlining the anti-TNF antibody to improve efficacy, reduce side effects, and ease administration.

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Safety of Infliximab and Other Biologic Agents in the Inflammatory Bowel Diseases

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The only biologic agent currently approved by the US Food and Drug Administration (FDA) for the treatment of inflammatory bowel disease (IBD) is the monoclonal chimeric antibody to tumor necrosis factor-α (TNF-α), infliximab (Remicade, Centocor, Malvern, Pennsylvania). This agent is approved for the induction and maintenance of remission of Crohn's disease (CD) not responsive to standard therapy, fistulizing CD, and ulcerative colitis not responsive to standard therapy [1]. Infliximab is also approved for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis [1]. Based on the results of several clinical trials recently presented [2–6], it is likely that two other TNF-α antagonists, adalimumab (Humira, Abbott Laboratories, North Chicago, Illinois) and certolizumab pegol (CDP870, Cimzia, UCB Pharma, Smyrna, Georgia), will be approved by the FDA for CD by mid-2007. Adalimumab is currently approved by the FDA as monotherapy or combination therapy for moderately to severely active RA and for psoriatic arthritis [7]. Furthermore, the monoclonal antibody to α_4-integrin, natalizumab (Tysabri, Elan Pharmaceuticals, San Diego, California, and Biogen Idec, Cambridge, Massachusetts), has recently been shown in a pivotal trial to be effective in the maintenance of remission of CD [8], and it is possible that this biologic agent will be approved for CD by 2007 or 2008. Serious neurologic sequelae have been reported following the use of this agent.

This article reviews the drug toxicity related to biologic therapy of IBD. Infusion reactions and antibodies to biologic therapies are discussed elsewhere in this issue. Adverse events following biologic agent therapy can be categorized

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into infectious, neurologic, cardiopulmonary, autoimmune, hematologic, gastrointestinal, hepatobiliary, and neoplastic. Preliminary data on the safety of these agents during pregnancy is also discussed.

CHALLENGES IN PHARMACOEPIDEMIOLOGY

Determining whether a particular adverse event is related to treatment can be surprisingly difficult, especially if the event of interest occurs infrequently. This determination can be even more problematic if the underlying diseases for which treatment is administered are systemic illnesses associated with complications in multiple organ systems, or if the conditions frequently require treatment with multiple agents. Unfortunately, all of these problematic situations hold true when referring to biologic agents: some of the more serious adverse events are low-frequency events; the conditions for which biologic agents are used are systemic and themselves associated with morbidity (eg, IBD, RA, multiple sclerosis [MS]); and many of the patients who are candidates for biologic agents are often already taking medications that can lead to adverse events (eg, thiopurines, methotrexate, β-interferon).

Well-designed studies of safety ideally have the following characteristics: (1) clearly identified groups similar with respect to important determinants of outcome; (2) similar measurements of exposure and outcome in the groups being compared; and (3) sufficiently complete follow-up [9]. The strongest level of evidence for determining whether an adverse event is linked to a particular medication is the randomized controlled trial. Trials, however, are powered to demonstrate efficacy, not safety; follow-up in most trials is relatively short; and an infrequent event may not be detected within the context of the trial. Large observational cohort studies (eg, phase IV registries) offer the opportunity to detect infrequent events, but the lack of randomization usually means that patients receiving the drug of interest have a higher disease severity than those not receiving the drug. Case-control studies are an efficient way to study putative associations, but the identification of proper controls, especially if the cases are not from a well-defined population, remains a continual challenge. Although case reports and case series may generate hypotheses, they are actually the weakest level of evidence for determining causality. All of these caveats must be kept in mind when interpreting safety data, the bulk of which actually falls into this last category. Finally, some of the better designed studies with respect to adverse events following biologic therapy have been published in the rheumatology literature. This is especially true for adalimumab, because this drug has been commercially available in the United States for RA (but not for CD) for several years. Unless otherwise stated, there is no reason to suspect differences in the risk of these adverse events across disease states; it seems reasonable to discuss some of the findings in RA.

INFECTIOUS ADVERSE EVENTS

Development of an infection is the most common adverse event reported following the use of TNF-α inhibitors [1,7]. For example, with an average

follow-up of 51 weeks, 36% of all patients receiving infliximab in clinical trials developed an infection, versus 25% of placebo-treated patients after an average follow-up of 37 weeks [1]. Most of these infections arose from the upper respiratory or urinary tract, were not serious, and were successfully treated. More serious infections, however, including pneumonia, sepsis, disseminated tuberculosis (TB), invasive fungal infections (eg, histoplasmosis or coccidioidomycosis), and other opportunistic infections (eg, pneumocystosis or listeriosis) have been reported after anti–TNF-α agent use. TNF-α seems to play a vital role in the formation of maintenance of granulomas, which themselves are critical in containing the aforementioned intracellular infections [10].

Part of the difficulty in determining causality is that many of the serious infections in patients treated with TNF-α inhibitors have occurred in patients on concomitant immunosuppressive therapy or corticosteroids that, in addition to their underlying CD, could predispose them to infections. It is not clear whether the increased risk of infections in these immune compromised patients is caused by their underlying chronic disease (with or without concomitant usage of corticosteroids and immunosuppressive agents), or if the risk can be attributed solely to the use of biologic agents. For example, in a preliminary report of a referral-based cohort from Cleveland Clinic, CD patients on immunosuppressives alone (azathioprine, 6-mercaptopurine, or methotrexate) were compared with those receiving infliximab, with or without immunosuppressives, for development of severe infection [11]. The frequency of severe infection was 4.6% in the immunosuppressive group and 5.2% in the infliximab group, but it is not clear if the median duration of follow-up was comparable in the two groups [11]. In a case-control study of opportunistic infections among IBD patients evaluated at Mayo Clinic, the odds ratios for opportunistic infection were 3.4 (95% confidence interval [CI], 1.8–6.2) with corticosteroids; 3.1 (95% CI, 1.7–5.5) with azathioprine–6-mercaptopurine; and 4.4 (95% CI, 1.2–17.1) with infliximab [12]. The odds ratio for opportunistic infection with any one of these drugs relative to none was 2.6 (95% CI, 1.4–4.7), and this increased to 12.9 (95% CI, 4.5–37) when two or more drugs were prescribed [12].

Studies of large registries may be helpful in sorting out some of the concerns raised in clinical trials or smaller case series. In a registry incorporating over 16,000 RA patients and over 36,000 person-years of follow-up, the hospitalization rate for pneumonia was 1.7% annually in the entire cohort [13]. In multivariate analysis incorporating numerous demographic and clinical factors, the only independent factors associated with pneumonia hospitalization were corticosteroid use, increasing age, underlying pulmonary disease, diabetes mellitus, and RA disease activity. TNF blockers were not independently associated with pneumonia [13]. In a registry of over 6000 CD patients followed for over 10,000 patient-years, the annualized incidence rate of serious infection within 3 months of infliximab infection was 1.3% versus 0.7% during observation not within 3 months of infusion, suggesting a doubling of risk [14]. After adjusting for disease activity and other medications, however, infliximab use was not associated with serious infection risk. Use of prednisone or

narcotics and moderate to severe disease activity were all independently associated with the risk of serious infection [14].

The TNF inhibitors as a class carry warnings in their prescribing information about the risk of serious infection [1,7,15]. These agents should not be administered to patients with a clinically important, active infection, and caution should be exercised when considering their use in patients with a chronic infection or a history of recurrent infection. For patients with CD, the most obvious scenarios in which to proceed very cautiously are treating patients with perianal or intra-abdominal infections, or patients with a phlegmonous process in the abdomen. For abscesses, drainage should be established before initiation of TNF-α blockade. Although the authors have no clinical data to back up this practice, they do not administer anti–TNF-α therapy to patients with intra-abdominal phlegmons until antibiotic coverage has been initiated, preferably for a week or two. Patients should be monitored for signs and symptoms of infection while on treatment with biologics. New infections should be closely monitored, and if a patient develops a serious infection, biologic therapy should be discontinued.

Tuberculosis

TB is the opportunistic infection most strongly associated with anti–TNF-α therapy. According to several reports, the risk of active TB in patients who are latently infected with *Mycobacterium tuberculosis* is increased after treatment with TNF-α inhibitors, and this topic has been the subject of several recent reviews [16–18]. Several cases of TB have been observed in randomized clinical trials of infliximab [19–21] and adalimumab [22,23]. By May 2001, a total of 70 cases of TB following anti–TNF-α therapy had been reported to the FDA through the MedWatch spontaneous reporting system [24]. A safety registry maintained by the Spanish Society of Rheumatology, which included over 1500 patients treated with anti–TNF-α drugs, estimated an annual TB incidence of 1% following initiation of infliximab, an incidence rate approximately 50 to 90 times higher than expected in the general Spanish population [25]. Fortunately, after widespread institution of TB screening in candidates for anti–TNF-α agents, the incidence rate declined [25]. A Swedish study suggested that RA patients on TNF blockers were four times more likely than RA patients not on TNF blockers to develop TB [26]. In a database of over 10,000 RA patients from the United States with over 16,000 person-years of follow-up, it was estimated that the incidence rate of TB in the pre-infliximab era was 6.2 cases per 100,000 person-years, but was as high as 52.5 per 100,000 among infliximab-treated patients, an eightfold elevation in risk [27]. Wallis and colleagues [28] used the MedWatch reporting system and manufacturers' estimates of the number of patients treated with infliximab and etanercept (a TNF-α blocker that is not effective for CD) through September 2002 to estimate incidence rates for TB of 53.8 cases per 100,000 person-years following initiation of infliximab, and 28.3 per 100,000 following initiation of etanercept [29,30]. There are clearly limitations in the ability of a spontaneous reporting

system, such as the FDA's, accurately to detect differences in adverse event risk across individual drugs [31,32]; however, these data are still consistent with other evidence that anti–TNF-α therapy is associated with TB risk.

The pattern of TB disease is often both unusual and severe in patients treated with TNF inhibitors. Both extrapulmonary and disseminated TB are more common in these patients than in immunocompetent patients [16,24]. These forms of TB are usually seen in association with significant immunosuppression. In a few instances, TB enteritis masquerading as CD was mistaken for and treated with infliximab, leading to a fatal outcome [33,34]. Most cases of TB have occurred within 2 to 4 months of starting anti–TNF-α therapy, and most cases have occurred in regions with a low incidence of TB [16,24]. These data suggest that most TB cases associated with TNF-α blockade are probably caused by reactivation of latent infection rather than newly acquired infection.

The risk of TB is now incorporated into the black-boxed warning section on the prescribing information for all commercially available anti–TNF-α agents [1,7,15]. In conjunction with a report of TB cases following TNF-α blockade in California, the Centers for Disease Control and Prevention published guidelines for the screening, diagnosis, and treatment of latent TB infection and active TB in candidates for such therapy [35]. Patients should be evaluated for latent TB infection with a tuberculin skin test. A tuberculin skin test result of $\geq$5 mm of induration should be considered positive; in such patients, active TB needs to be excluded (with a chest radiograph at a minimum). It should be recognized that a negative tuberculin skin test does not exclude the possibility of latent TB infection, because many if not most patients who are candidates for TNF blockade are anergic [36], and empiric treatment of latent TB infection should be considered in high-risk groups even if the tuberculin skin test is negative (eg, prisoners, homeless, birth in a high-incidence country, and so forth) [35]. Treatment of latent TB infection should be initiated before therapy with a TNF-α antagonist, preferably with 9 months of isoniazid [35]. There is no consensus on how long latent TB infection should be treated before anti–TNF-α therapy can be initiated. Once TNF blockade has been initiated, clinicians should have a high index of suspicion for TB in any patient who has a febrile or respiratory illness. If active TB is diagnosed while on anti-TNF therapy, the latter should be discontinued until treatment for active TB has been initiated and the patient's condition has improved [35]. Exactly when anti-TNF therapy can be resumed in these patients is still not settled, but caution should be exercised.

Nontuberculous Bacterial Infections

It is difficult to determine if the infections are more likely to occur because of TNF blockage itself, the underlying disease, or the concomitant immunosuppression. The infections most frequently reported in clinical trials of anti–TNF-α agents were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis), but these did not occur significantly more frequently than in placebo-treated patients [6,21,37–41]. Serious infections reported after TNF

blockade include pneumonia [6,42–44], cellulitis [44], urinary tract infection, skin infection [43], staphylococcal sepsis [45], and fatal infections [41,44,46]. *Listeria monocytogenes* infections of the bloodstream and central nervous system have been reported [47–52]. By September 2002, 18 cases of listeriosis following TNF blockade, several of which were fatal, had been reported to the FDA [29,30,53]. Most patients were on concomitant immunosuppression.

Abscesses (perianal, peristomal [39,42], and abdominal [37,41,44]) are another serious complication. In a randomized, double-blind, placebo-controlled study of 94 patients evaluating the safety and efficacy of infliximab for fistulizing CD, 12% of patients in the treatment arm developed an abscess in the area of fistulas between 8 and 16 weeks after the last infusion of infliximab, compared with 3.5% of patients in the placebo group [39].

Invasive Fungal Infections

Invasive opportunistic fungal infections that have been reported following anti–TNF-α treatment include histoplasmosis [44,54,55], coccidioidomycosis [29], systemic candidiasis [56], *Pneumocystis jiroveci (carinii)* pneumonia [52,57–60], invasive pulmonary aspergillosis [61–63], disseminated sporotrichosis [64], nocardiasis [41,65], and cryptococcosis [66,67]. By September 2002, the FDA had received through the MedWatch system numerous reports of invasive fungal infections in United States patients following anti–TNF-α therapy, including 40 cases of histoplasmosis, 26 cases of candidiasis, 24 cases of aspergillosis, 18 cases of cryptococcosis, and 12 cases of coccidioidomycosis [30].

Among cases of histoplasmosis associated with TNF-α blockade in the United States, most patients resided in or were raised in areas endemic for histoplasmosis (Ohio and Mississippi River valleys), and virtually all were receiving other immunosuppressive agents [54,55]. Similarly, symptomatic coccidioidomycosis following anti–TNF-α therapy has been for the most part reported in the endemic areas of Arizona, California, and Nevada, and virtually all patients have been reported to be on concomitant immunosuppression [68]. For patients who have resided or are currently residing in regions where histoplasmosis or coccidioidomycosis are endemic, the benefits and risks of treatment should be carefully considered before initiation of anti–TNF-α therapy, and patients should be advised to have a low threshold for seeking medical attention for febrile or pulmonary symptoms. At this juncture, there is no evidence to recommend obtaining *Histoplasma capsulatum* or *Coccidioides immitis* serologies in residents of endemic areas in advance of anti–TNF-α therapy.

Viral Infections

Viral infections, including herpes simplex, primary varicella infection, herpes zoster, and cytomegalovirus infection, have been reported following anti–TNF-α therapy [42,49,61,69,70]. In some cases, such as disseminated cytomegalovirus or varicella infection, these have been life-threatening [41,71]. In a small prospective study of RA patients who were tested serially for viral loads for cytomegalovirus, Epstein-Barr virus, and human herpesvirus-6, however,

infliximab did not result in reactivation of any lymphotropic herpesvirus, suggesting that prophylactic treatment of latent infection is not warranted [72].

NEUROLOGIC ADVERSE EVENTS

An anti–TNF-α agent, lenercept, was administered in a placebo-controlled randomized trial for treatment of MS, and patients treated with active drug experienced more MS exacerbations than placebo-treated patients [73]. Infliximab and other agents that inhibit TNF-α have been associated with new onset or exacerbation of clinical symptoms or radiographic evidence of central nervous system demyelinating disorders, including MS [41,74–76]. Mohan and colleagues [74] used the FDA MedWatch system to identify 19 cases of demyelinating events occurring following administration of anti–TNF-α agents as of early 2001. Symptoms included paresthesia, dysesthesia, cognitive dysfunction, ocular symptoms, difficulty walking, extremity weakness, incontinence, and hemiparesis. Fortunately, in most cases, symptoms improved or resolved following cessation of therapy. Central nervous system adverse events have been reported more commonly with etanercept compared with infliximab [74]. Rare cases of optic neuritis [77,78], bilateral optic neuropathy [79], and aseptic meningitis [80] have also been reported. A recent safety assessment of adalimumab based on clinical trials and postmarketing surveillance of RA patients estimated an annual incidence of demyelinating disorders following adalimumab therapy of approximately 1 per 1000 patient-years [81]. The prescribing information for all of the currently available anti–TNF-α agents contains warnings about neurologic events, and it is necessary to use caution while considering the use of anti–TNF-α drugs in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders [1,7,15]. It is probably not safe to continue use or readminister drug to patients who develop significant central nervous system adverse reactions. Although there is evidence to suggest that demyelinating diseases occur more commonly in patients with IBD than among those without IBD [82], the temporal relationship of these events to initiation of anti–TNF-α therapy, and the improvement or resolution of symptoms following cessation of therapy, suggests a causative relationship.

Other neurologic events have been reported following anti–TNF-α therapy, including motor neuropathy with conduction blocks following infliximab therapy [83,84] and lower-extremity paresthesia and foot drop following adalimumab therapy [85].

CONGESTIVE HEART FAILURE

Based on the observations that TNF-α levels were elevated in congestive heart failure (CHF) patients, and that etanercept seemed beneficial in moderate to severe CHF patients in a small pilot study, the randomized Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial was undertaken [86]. ATTACH evaluated the use of infliximab (5 or 10 mg/kg) or placebo in patients with New York Heart Association class III or IV heart failure and left

ventricular ejection fraction ≤35%. There was no benefit derived from infliximab during the study period; the combined risk of death from any cause or hospitalization for heart failure through 28 weeks was increased in patients randomized to infliximab, 10 mg/kg (hazards ratio, 2.8; 95% CI, 1–8) [86]. There have been numerous postmarketing reports of worsening CHF, with and without identifiable precipitating factors, reported through FDA's MedWatch. Of the 47 reported cases as of August 2002, 38 were new and 9 were exacerbations [87]. Of the 38 new cases of heart failure, one half had no identifiable risk factors, and 10 patients were <50 years old. Discontinuation of anti–TNF-α therapy led to either resolution or improvement in CHF, apart from death in one patient [87]. A safety update of adalimumab in clinical trials and postmarketing surveillance of RA patients reported an incidence of CHF of approximately three cases per 1000 patient-years [81]. It is difficult to know whether some of these cases could be explained by an underlying disease, such as RA, which is known to have multiple comorbidities. A registry of over 13,000 RA patients and over 2500 osteoarthritis patients detected a higher prevalence of CHF among RA patients (3.9%) than osteoarthritis patients (2.3%), but the prevalence of CHF in RA patients treated with anti–TNF-α therapies was slightly lower than in those not treated (3.1% versus 3.8%) [88].

The infliximab prescribing information contains a warning regarding the use of infliximab in patients with known CHF [1], and the adalimumab prescribing information contains a precaution [7]. Infliximab at a dose of greater than 5 mg/kg is contraindicated in patients with moderate to severe CHF, and it is recommended that infliximab should be used in patients with heart failure only after consideration of other treatment options [1]. These patients should be closely monitored during therapy, and infliximab should be discontinued if new or worsening symptoms of heart failure appear.

THROMBOSIS

A case of extensive deep vein thrombosis of the forearm developing one day after receiving an infusion of infliximab intravenously in that arm has been reported [89]. There are also case reports of retinal vein thrombosis [90], paroxysmal nocturnal hemoglobinuria with Budd-Chiari syndrome [91], and pulmonary thromboembolism [43,52] associated with its use.

LYMPHOMA AND OTHER MALIGNANCIES

Sorting out whether anti-TNF therapy is linked to the development of lymphoma or other malignancies is difficult for the same reasons mentioned previously: the underlying disease states for which anti-TNF therapy is administered may be associated with an increased cancer risk, and concomitant immunosuppression may play a role. In clinical trials, infliximab-treated patients had a higher incidence of lymphomas (0.11 cases per 100 patient-years) compared with placebo-treated patients (0 cases) [1]. The former incidence rate was estimated to be five times higher than what would have been expected in the general population [1]. The incidence rate of lymphomas in clinical trials of adalimumab in RA

patients was 0.21 cases per 100 patient-years, which again was estimated to be about five times higher than expected in the age-matched general population [7]. In a more recent safety update of adalimumab, the incidence rate of lymphoma in RA with over 12,000 patient-years of follow-up was 0.12 cases per 100 patient-years, a threefold elevation of risk [81]. This elevation in relative risk is only slightly higher than the elevated relative risk of lymphoma seen in RA patients overall [92]. In one of the few studies that compared two cohorts of RA patients, one receiving anti-TNF therapy and the other not, a study from Malmö, Sweden, showed that RA patients treated with anti-TNF therapy experienced a lymphoma rate 11 times higher than expected in the general population, whereas RA patients not treated with these agents experienced a lymphoma rate very similar to what would have been expected [93].

Unlike the situation with RA, most population-based studies of CD have not demonstrated an elevated risk of lymphoma among all Crohn's patients. In a Swedish cohort of 217 residents of Stockholm County with CD treated with infliximab, Ljung and colleagues [52] identified three patients who developed lymphoma (of which two were fatal). The overall annual incidence of lymphoma was 1.5% in this cohort, compared with the overall population-based value of 0.015% in the background Swedish population. One of the three patients had been on concomitant azathioprine [52], which is likely associated with a threefold elevation in risk of lymphoma in IBD [94]. More reassuring results were noted in the large TREAT registry. Over 6000 CD patients, approximately half of whom have received infliximab, have been followed for an average of 1.9 years [14]. The incidence rate of lymphoma in the cohort who had received infliximab was 0.62 cases per 1000 person-years, versus 0.57 cases per 1000 in the group not receiving infliximab. Considering the effect on lymphoma risk from other forms of immunosuppression, it seems to be biologically plausible that anti–TNF-α therapy is associated with an increased relative risk of lymphoma. The highest estimate of the absolute risk is 1.5% annually [52], but this is an outlier, and most other estimates are in the range of 0.6 to 2 cases per 1000 person-years. The risk ranges from 1 case per 500 person-years to 1 per 1600 person-years.

Whether the overall risk of malignancy is elevated following TNF blockade is unclear. In the controlled portions of clinical trials with infliximab, the overall cancer rate was 0.65 cases per 100 patient-years, which was five times higher than the rate in the placebo-treated patients [1]. This rate was actually similar, however, to what would have been expected in the general population. In a randomized controlled trial of infliximab in patients with chronic obstructive pulmonary disease, the incidence rate of cancer was 7.7 cases per 100 person-years in the active treatment arm versus 1.6 per 100 in the placebo arm [1]. Most of the cancers were bronchogenic or head and neck cancers. Other malignancies, such as rectal cancer [41], cutaneous T-cell lymphoma [95], and squamous cell cancer of skin [96] have also been reported in patients treated with infliximab, but the incidence rate of these cancers was similar to what would be expected in the general population. The prescribing information for infliximab states that

caution should be exercised in considering this treatment in patients with a history of malignancy or continuing the treatment in patients who develop malignancy [1].

AUTOIMMUNITY AND LUPUS-LIKE SYNDROME

The immunogenicity of anti–TNF-α agents is described elsewhere in this issue. The development of antinuclear antibodies, anti–double stranded DNA antibodies, and anticardiolipin antibodies has been observed after treatment with anti–TNF-α therapy [37,39]. Fortunately, the incidence of clinically significant drug-induced systemic lupus erythematosus is much lower. In a Belgian program of expanded access to infliximab for CD, the cumulative incidence of antinuclear antibodies positivity in 125 patients was 57% at 24 months [97]. Almost half of these patients developed antinuclear antibodies after the first infusion. Among 43 patients with antinuclear antibodies titers $\geq$1:80, 33% had anti–double stranded DNA and 21% had antihistone antibodies [97]. Two patients with both anti–double stranded DNA and antihistone antibodies developed drug-induced lupus, and one developed autoimmune hemolytic anemia. Women were three times more likely, and those with a butterfly or papulosquamous rash were 10 times more likely, to have antinuclear antibodies [97]. There was a weak relationship between the antinuclear antibodies and antibodies to infliximab. In clinical trials of maintenance therapy with infliximab, the prevalence of antinuclear antibodies and anti–double stranded DNA has been higher in patients in active treatment arms than in placebo arms [40,41]; however, the incidence of clinically evident lupus-like syndromes has remained quite low. A French group systematically sought for evidence of other autoantibodies in a series of 35 CD patients treated with infliximab, but could find only a few patients positive for autoantibodies other than antinuclear antibodies or anti–double stranded DNA [98]. A recent safety update of adalimumab in RA patients noted an incidence rate of systemic lupus erythematosus or lupus-like syndrome of approximately 0.1 cases per 100 patient-years in the clinical trials and 0.03 cases per 100 patient-years in postmarketing surveillance [81]. The clinical significance of asymptomatic antinuclear antibodies or anti–double stranded DNA positivity remains unclear. The possibility of autoimmunity is mentioned in the precautions sections of the prescribing information of both infliximab and adalimumab [1,7]. Treatment with these agents should be discontinued in patients who develop symptoms consistent with systemic lupus erythematosus or lupus-like syndrome.

HEMATOLOGIC EVENTS

Rare reports exist of anemia, leukopenia, neutropenia, thrombocytopenia, or pancytopenia following anti–TNF-α therapy, some with a fatal outcome [19,99–102]. The causal relationship of these events to anti-TNF therapy remains unclear. The incidence of blood dyscrasias in a recent safety update of adalimumab in RA patients was approximately 1 per 1000 patient-years in postmarketing surveillance [81]. The warnings sections of the prescribing

information for both infliximab and adalimumab suggest exercising caution in patients who have an ongoing or a history of significant hematologic abnormalities, and discontinuing therapy if significant hematologic abnormalities develop [1,7]. A potential drug interaction between infliximab and azathioprine has also been demonstrated in CD patients [103]. CD patients on maintenance azathioprine had an elevation in their erythrocyte 6-thioguanine levels 1 to 3 weeks after infliximab infusion. The increase in 6-thioguanine levels corresponded with a good response to infliximab infusion [103]. These same metabolites may influence leukocyte counts, however, so patients on azathioprine or 6-mercaptopurine should continue to be monitored for leukopenia once infliximab has been added to their regimen.

HEPATOBILIARY AND GASTROINTESTINAL

A variety of hepatobiliary events following anti–TNF-α therapy have been reported in either case reports or in the prescribing information for these medications [1,7]. These events include cholestatic hepatic injury [104], acute nonobstructive cholecystitis [105], and fulminant hepatitis in a patient with hepatitis B and Still's disease, [106]. The prescribing information for infliximab refers to cases of severe hepatic reactions, including acute liver failure, which occurred between 2 weeks and over a year after initiation of therapy [1]. Some cases were fatal or required liver transplantation. It is recommended that infliximab be discontinued in patients with liver test abnormalities greater than five times the upper limit of normal [1].

Reactivation of hepatitis B in chronic carriers has been reported following infliximab therapy [1]. In a prospective study of CD patients receiving infliximab, three patients with chronic hepatitis B virus infection were identified [107]. Two of the three developed severe reactivation of chronic hepatitis B virus after infliximab was withdrawn, and one patient died [107]. The patient who did not develop reactivation had been treated with lamivudine, and the authors suggested that prophylaxis of reactivation should be considered in all chronic hepatitis B virus patients who are candidates for infliximab [107]. Chronic carriers need to be monitored carefully before initiation of and during anti-TNF therapy.

Cases of duodenal ulcer perforation, small bowel perforation [108], intestinal obstruction [37,39], and pancreatitis [109] have been described in patients being treated with infliximab. Whether infliximab has a causal role in these adverse events is not known.

PREGNANCY

Infliximab and adalimumab are categorized by the FDA as pregnancy risk category B medications [1,7]. Limited data are available on the safety of infliximab in pregnancy, because there are no controlled studies in pregnant women. In a safety database maintained by the manufacturer of infliximab, pregnancy outcome data on 96 women who were exposed to infliximab were available [110]. Live births occurred in 67%, miscarriages in 15%, and termination of

the pregnancy occurred in 19%. These outcomes were quite similar to that reported for all United States white women between 1976 and 1996 by the National Center for Health Statistics [110]. Two fetal anomalies, tetralogy of Fallot and intestinal malrotation, were reported in this series. Infliximab was used intentionally during pregnancy in 10 women with CD without any congenital malformations or intrauterine growth retardation [111]. Three infants were premature and one had low birth weight. In one case report, a 26-year-old woman with active CD received two infusions of infliximab at approximately week 1 and week 3 after conception [112]. The baby was born prematurely at week 24 of conception and died of complications on the third day after birth. The patient was also receiving azathioprine, metronidazole, and mesalamine at the time of conception. The role of infliximab in the outcome of this pregnancy was unclear.

Maintenance adalimumab use during pregnancy in a patient with CD was recently reported [113]. The pregnancy was uncomplicated and the child was reported as healthy at birth and at 6 months of age. There is also another case report from the Spanish literature of a term pregnancy in a patient with CD receiving treatment with adalimumab [114].

MISCELLANEOUS

Rare cases of ureteral obstruction [39], acute respiratory distress syndrome [115], diffuse alveolar hemorrhage [116], bullous skin lesions [117], and psoriasiform eruption [118] have also been reported following anti-TNF agents. Whether a causal relationship exists, remains unclear.

NATALIZUMAB

In a pilot study of treatment of active ulcerative colitis with natalizumab, no adverse events related to the drug were reported [119]. In the ENACT-1 and ENACT-2 trials of natalizumab for CD, subjects in the natalizumab treatment group had a significantly higher incidence of influenza and influenza-like illness compared with the placebo group [8]. One case each of varicella pneumonia and cytomegalovirus hepatitis occurred in the natalizumab-treated group. In two earlier randomized controlled trials of natalizumab for the treatment of CD, the rate of serious adverse events was similar in both the treatment and placebo groups [120,121].

It was later reported that a fatal case of JC virus-induced progressive multifocal leukoencephalopathy had developed in a subject with CD treated with natalizumab during the ENACT-1 and ENACT-2 trials [122]. This patient was originally thought to have died of an astrocytoma, but the progressive multifocal leukoencephalopathy was diagnosed in retrospect after two patients with MS who had been treated with natalizumab also developed progressive multifocal leukoencephalopathy [123,124]. The drug was voluntarily withdrawn from the market for MS after these reports. In a comprehensive follow-up study of over 3100 patients who had received natalizumab in clinical trials, which included measurement of plasma viral load of JC virus, brain MRI, and, if

indicated, cerebrospinal fluid JC viral load, no additional cases of progressive multifocal leukoencephalopathy were detected [125]. It was estimated that the incidence of progressive multifocal leukoencephalopathy in natalizumab-treated patients was 1 case per 1000 treated patients (95% CI, 0.2–2.8 per 1000 patients). It will likely return on a limited basis for MS, and whether or not this drug will eventually be approved for use in CD is unclear.

SUMMARY

In many ways, infliximab has drastically altered expectations for medical therapy in IBD, and it is expected that adalimumab and certolizumab pegol will ultimately have a similar role. Patients initiating such therapy should be made cognizant of the potential risks of serious infection including opportunistic ones, such as TB and histoplasmosis; demyelinating disorders; CHF; and lymphoma. Proper selection of candidates for anti–TNF-α therapy is critical in maintaining a proper benefit-to-risk ratio.

ADDENDUM

After submission of this article in March 2006, several important events relative to this topic have occurred. In May 2006, the manufacturer of infliximab amended the black-boxed warning in the prescribing information to include information about the risk of hepatosplenic T-cell lymphoma in adolescent and young adult patients with CD [1]. Six CD patients, five of whom were adolescents and all of whom were treated with both infliximab and thiopurine, have developed this rare tumor, among approximately 10,000 pediatric CD patients who have received infliximab between 1998 and 2005. The tumor is aggressive and, in most cases, fatal. More recently, an analytical model incorporating the risks (eg, lymphoma, death) and benefits (eg, remission, fewer surgeries, improved quality of life) of infliximab therapy in CD was published [126]. If 100,000 CD patients treated with infliximab were compared with 100,000 treated with conventional therapy, at the end of 1 year the infliximab treated cohort would have 12,216 more patients in remission, 4255 fewer surgeries, and 33 fewer Crohn's-related deaths. However, this would occur at the cost of 201 more lymphomas and 249 more deaths (related to infliximab). Despite this increased death rate, the over all improvement in quality of life would result in more quality-adjusted life years per patient in the infliximab treated group [126].

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Infusion reactions and their management

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Infliximab (Remicade), a chimeric mouse-human IgG1 monoclonal antibody, is a major advance in the treatment of immune-mediated inflammatory diseases, such as rheumatoid arthritis, psoriasis, and Crohn's disease (CD). It binds to both soluble and transmembrane human tumor necrosis factor-α with high affinity and specificity. By blocking the binding of the factor to the p55 and p75 receptors, it neutralizes the functional activity of tumor necrosis factor-α in a variety of bioassays. Infliximab was approved for the treatment of Crohn's in 1998 and for ulcerative colitis in 2005.

As in the case with any foreign protein–derived agent, infusion of infliximab can lead to the formation of antibodies to infliximab (ATI), which may play a role in the development of infusion reactions [1–3]. Overall, these reactions are rare, occurring in approximately 5% to 10% of all infusions [1], and they can, in most cases, be easily managed [4]. The presence of ATI may also limit infliximab's long-term efficacy [2,3]. New infusion protocols have been developed, however, which may minimize such antibody formation and mitigate its potentially negative effects. Such methods should be considered for all infliximab infusions to maximize the efficacy of infliximab and minimize the potential side effects associated with antibody formation.

IMMUNOLOGIC RESPONSE TO MONOCLONAL ANTIBODIES

The human immune system can react to monoclonal antibodies as foreign antigens by producing its own antibodies to different epitopes on the molecule. It can produce anti-idiotypic, antiallotypic, or antimouse antibodies to the Fv region, the Fc region, or murine epitopes, respectively. Antibodies against infliximab were initially called "human antichimeric antibodies" and are now known as "antibodies to infliximab." As expected, monoclonal antibodies comprised entirely of murine protein are more immunogenic than completely

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human monoclonal antibodies. Even completely human monoclonal antibodies can trigger an immune response, however, leading to the development of human antihuman antibodies.

MEASURING ANTIBODIES TO INFLIXIMAB

Two companies, Centocor (Malvern, Pennsylvania) and Prometheus (San Diego, California), have developed assays for the detection of ATI. The Centocor assay measures both anti-idiotypic and antimurine Ig antibodies to epitopes on the murine variable region of infliximab and antiallotypic antibodies to the human IgG1 constant region. When competitive inhibition with the addition of human IgG1 was performed, antiallotypic antibodies were not found [5]. The Prometheus assay is polyclonal; however, it is not reported whether they are anti-idiotypic antibodies, antiallotypic antibodies, nonspecific antibodies that cross-react with other chimeric antibodies, or some combination of the above. No studies comparing the assay characteristics of the Centocor and Prometheus ATI assays have been reported. Infliximab itself interferes with the Centocor ATI assays; the presence of ATI can only be determined when infliximab is not present in the serum. When infliximab is found, the sample is considered indeterminate. It may be reasonable to consider samples indeterminate for ATI as negative, because even if present, these ATI are present in small amounts relative to the infliximab that is present in excess [5].

PREVALENCE OF ANTIBODIES TO INFLIXIMAB

The formation of ATI is not uncommon. The frequency in the literature varies widely from 6% to 61% but is generally 6% to 15% [1,2,6–10]. This broad range is at least partially attributable to the different ATI assays used in the studies, to different infliximab dosing schedules, and to variations in concomitantly administered medications. As discussed later, infliximab is much more immunogenic when given as a single induction dose, episodic treatment, and monotherapy without a concurrent immunomodulator. Furthermore, premedication with hydrocortisone can reduce ATI levels.

Single Versus Three Induction Infusions

Best available evidence supports the observation that infliximab is more immunogenic when given as a single induction infusion. In the early phase 2 trial, infliximab was administered as a single-dose infusion, and nonresponders received an open label dose of infliximab, 10 mg/kg, at week 4 [7]. All responding patients were rerandomized at week 12 into a 36-week retreatment study of infliximab, 10 mg/kg, every 8 weeks [8]. Altogether, 60 of 102 patients who received infliximab could be assessed for ATI, of whom 10 (16%) were positive [7]. This is in contrast to the placebo-controlled phase 3 trial in which infliximab was administered as three induction infusions at 0, 2, and 6 weeks. Fifty of 63 patients who received infliximab could be assessed for ATI, of whom three (6%) were positive [6]. This finding was confirmed later in ACCENT I [1], which was a large phase 4 randomized controlled trial designed to assess the efficacy and safety of repeated

infliximab infusions. Patients were randomized to receive episodic infliximab or a 0-, 2-, or 6-week induction regimen followed by a scheduled infusion every 8 weeks with crossover to increased dose episodic infusions for treatment failures. Because of the maintenance regimen, many patients still had infliximab in their serum, and only 237 of 442 patients could be assessed for ATI. At week 54, 64 patients (27%) had ATI overall [1]. Through week 72, ATI could be assessed in 514 patients and were detected in 30% of patients who received a single induction dose versus 10% and 7% of patients who received three dose and maintenance, 5 mg/kg and 10 mg/kg, respectively ($P < .0001$) [11]. In a small prospective observational study, Farrell and colleagues [3] found the administration of a second infliximab infusion within 8 weeks of the first dose was a significant protective factor against ATI formation.

In contrast, Baert and colleagues [2] prospectively followed 125 CD patients who received a single 5 mg/kg induction dose or three 5 mg/kg induction doses at 0, 2, and 6 weeks. Antibodies to infliximab were detected in 61% of patients overall, and a three-dose induction regimen did not decrease ATI formation and was actually slightly worse than single induction treatment. This was a smaller observational study, however, and used the Prometheus assay for ATI detection.

Episodic Versus Maintenance Regimen

Episodic or on-demand treatment with infliximab was more immunogenic than scheduled maintenance therapy. The ACCENT I trial showed that a three-dose induction regimen followed by maintenance therapy was the least immunogenic compared with single-dose induction followed by episodic treatment (ATI present in 28% versus 6%–9%, respectively) [12]. It also seems that the three-dose induction and maintenance regimen is slightly better than the addition of an immunomodulator for preventing antibody formation. The absolute benefit of adding immunomodulators to maintenance dosing was only 4% (ATI rates of 11% versus 7%) [1].

Concomitant Immunosuppressive Therapy

Concurrent therapy with 6-mercaptopurine, azathioprine, methotrexate, or steroids reduces ATI formation. Combining all early trials for CD [6–8], 134 of 199 patients who received infliximab could be assessed for ATI of whom 18 (13%) were positive overall. Ninety-nine of these 134 patients were concomitantly treated with immunomodulators, of whom 10 (10%) developed ATI. In contrast, 35 of 134 patients received infliximab monotherapy, of whom eight (23%) developed ATI. This finding was confirmed in the ACCENT I trial, in which patients receiving immunomodulators had a lower incidence of ATI compared with patients on infliximab monotherapy (10% and 18%, respectively; $P = 0.02$) [11]. The frequency of ATI formation was also less in patients receiving both steroids and immunomodulators (6%) than in patients on immunomodulators alone (10%); patients on steroids alone (17%); and patients receiving neither (18%). In the ACCENT II trial, 17% of patients developed ATI. This trial also demonstrated that patients who were

on steroids (13%) or immunomodulators (11%) were less likely to develop antibodies than patients on infliximab monotherapy (24%). Patients who were on both steroids and immunomodulators were the least likely to develop ATI (4%) [10].

Premedication with Hydrocortisone

Farrell and colleagues [3] randomized 80 consecutive patients beginning infliximab treatment to premedication with 200 mg intravenous hydrocortisone or placebo before each infliximab infusion. The primary end point, predefined as the reduction in median ATI concentration levels at week 16, was met (1.6 versus 3.4 μg/mL; $P = 0.02$). Hydrocortisone premedication did not significantly reduce ATI formation, although at weeks 8 and 16 postinfusion the hydrocortisone groups had fewer ATI-positive patients (21% versus 29% $P = 0.14$; and 26% versus 42%, $P = 0.06$). Premedication with hydrocortisone can be considered, especially in patients on infliximab monotherapy (eg, because of intolerance of concomitant immunomodulators) or in patients just starting on concurrent immunomodulators.

CLINICAL SIGNIFICANCE OF ANTIBODIES TO INFLIXIMAB

Although antibodies are formed against infliximab, it is not clear that this truly has clinical significance. Antibodies to infliximab may decrease clinical efficacy if anti-idiotypic antibodies neutralize the monoclonal antibody by binding to the Fv region of the molecule or if antiallotypic antibodies promote the clearance of the monoclonal antibody by binding to the Fc region. In addition to decreased efficacy of the drug over time, there may be a correlation between antibody formation and an increased risk of infusion reactions.

Infusion Reactions

Infusion reactions to infliximab or against any monoclonal antibody can be characterized as either acute or delayed. An acute infusion reaction occurs within 24 hours of an infliximab infusion, but most commonly within 10 minutes to 4 hours of the infusion. A delayed infusion reaction can occur from 1 to 14 days after infusion, but usually occurs after 5 to 7 days. Both types of reactions can be further characterized as mild, moderate, or severe, depending on the accompanying signs and symptoms (Table 1).

Acute infusion reactions can be further characterized by whether they are immune-mediated or nonallergic based. Anaphylaxis is mediated by antigen-induced IgE-mediated mast cell and basophil degranulation, whereas an anaphylactoid reaction results from the direct release of mediators from mast cells and basophils. Symptoms of a true allergic anaphylactic reaction include chest tightness, shortness of breath, flushing, hypotension, wheezing, tachycardia, and urticaria. Without bronchospasm or urticaria, an acute infusion reaction is unlikely to be a true type I–mediated hypersensitivity reaction and should be considered nonallergic or anaphylactoid. The nonallergic types of reactions make up most acute infusion reactions. IgE-mediated reactions to infliximab are quite rare.

Table 1
Infliximab infusion reaction protocol

Type of reaction symptoms	Treatment protocol	Prophylaxis
Mild		
Flushing, dizziness, headache, diaphoresis, nausea, or palpitations	Slow infusion rate to 10 mL/h Infuse normal saline (500–1000 mL/h) Diphenhydramine 25–50 mg IVPB Acetaminophen 650 mg po Monitor VS every 10 min until WNL Wait 20 min, then increase infusion rate to 20 mL/h × 15 min, then 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated	Pretreat with diphenhydramine 25–50 mg and acetaminophen 650 mg po 1.5 h before infusion (5 days of a second-generation antihistamine can be substituted to decrease sedation) Test dose at 10 mL/h × 15 min then increase to 20 mL/h, 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min as tolerated
Moderate		
Chest discomfort, dyspnea, hypotension or hypertension (>20 mm Hg SBP), increased temperature, palpitations, or urticaria	Stop infusion or slow infusion to 10 mL/h Infuse normal salie (500–1000 mL) Diphenhydramine 25–50 mg IV Acetaminophen 651 mg po Monitor VS every 5 min until WNL Wait 20 min then restart infusion at 10 mL/h for 15 min Increase infusion rate to 20 mL/h × 15 min, then 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min as tolerated	Pretreat with diphenhydramine 25–50 mg and acetaminophen 650 mg po 1.5 h before infusion (5 days of a second-generation antihistamine can be substituted to decrease sedation) Test dose at 10 mL/h before × 15 min Increase infusion rate to 20 mL/h, 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min as tolerated
Severe		
Hypotension or hypertension, increased temperature with rigors, dyspnea with wheezing, stridor, flushing	Stop infusion Maintain airway; oxygen is available Epinephrine (1:1000) 0.1–0.5 mL SQ (may repeat every 5 min × 3) if wheezing present Dephenhydramine 25–50 mg IVPB hydrocortisone 100 mg IV or methylpredinsolone 20–40 mg IV Monitor VS every 2 min until WNL	Prednisone 50 mg po every 12 h for three doses before infusion or hydrocortisone 100 mg IV or methylprednisolone 20–40 mg IV before infusion Pretreat with diphenhydramine 25–50 mg and acetaminophen 650 mg po 1.5 h before infusion (5 days of a second-generation antihistamine can be substituted to decrease sedation) Test dose at 10 mL/h before for 15 min Increase infusion rate to 20 mL/h, 40 mL/h, 80 mL/h, 100 mL/h every 15 min as tolerated

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Table 1
(*continued*)

Type of reaction symptoms	Treatment protocol	Prophylaxis
Delayed		
Rash or urticaria, myalgias, flu-like symptoms, joint stiffness and pain, headache	Acetaminophen 650–1000 mg po qid Second-generation antihistamine or diphenhydramine 50 mg po qd-bid methylprednisolone pack if severe arthralgia	Pretreat with diphenhydramine 25–50 mg and acetaminophen 650 mg po 1.5 h before infusion (5 days of a second-generation antihistamine can be substituted to decrease sedation Test dose at 10 mL/h before for 15 min Increase rate to infuse over 3 h Acetaminophen 650–1000 mg po qid for 3 d Second-generation antihistamine for 7 d following infusion Send home with methylprednisolone dose pack if severe joint pain

Abbreviations: IV, intravenous; IVPB, intravenous piggy back; SBP, systolic blood pressure; SQ, subcutaneous; VS, vital signs; WNL, within normal limits.

To date, only one study has examined the pathogenesis of acute infusion reactions [4]. Serum was obtained from 11 patients who had a total of 14 acute infusion reactions. The serum level of tryptase, a mast cell enzyme elevated after an anaphylactic reaction, was measured and found to be within the normal range in all cases. Levels of IgE were measured in six of these patients and found to be normal. It was concluded that these acute infusion reactions were not caused by IgE-mediated hypersensitivity. This probably explains why most of the reactions were successfully managed by simply reducing the rate of infusion. If these had been IgE-mediated anaphylactic reactions, reinfusion would have been impossible.

Antibodies to infliximab have been associated with an increased risk of infusion reactions. In the ACCENT I trial [1], 42 (16%) of 254 infusions resulted in infusion reactions among patients positive for ATI compared with 55 (8%) of 656 and 47 (3%) of 1470 in patients negative for ATI and with indeterminate status, respectively. Thirty-eight percent of patients positive for ATI had one or more infusion reactions, compared with 24% of patients negative for ATI. Antibodies were associated with a 12% absolute increase in infusion reactions but no increase in serious infusion reactions. Infusion reactions leading to discontinuation of infliximab occurred in 6% of ATI-positive patients and 2% of ATI-negative patients. Similar trends were seen in the study by Farrell and coworkers [3], in which patients who had ATI were more likely to develop an infusion reaction. Overall, ATI were seen in 36% of their patients (19 of 53).

Seven of 53 patients experienced serious infusion reactions requiring the discontinuation of infliximab. All seven (100%) patients were positive for ATI. Interestingly, pretreatment with hydrocortisone had no effect on the number of infusion reactions.

In ACCENT I [11], higher antibody titers were not found to be associated with more infusion reactions. This is in contrast to the study by Baert and coworkers [2], which demonstrated a strong correlation between the concentration of ATI and the occurrence of an infusion reaction. The median concentration was 20.1 μg/mL at the time of a first infusion reaction, as compared with 3.2 μg/mL among patients without an infusion reaction. Concentrations of 8 μg/mL or higher were suggested to predict a higher risk of infusion reaction (relative risk 2.4).

Delayed infusion reactions are characterized by a skin rash, diffuse joint pains, fatigue, and myalgias, with or without fever. These reactions have been labeled "serum-sickness like" and may actually represent mild type III immune complex–mediated reactions. In contrast to true type III reactions, delayed infusion reactions to infliximab have not resulted in end-organ damage, such as renal failure, arthritis, or pneumonitis. These reactions must be differentiated from other states that may produce similar symptoms, such as a flare of inflammatory bowel disease, extraintestinal manifestations of inflammatory bowel disease, a viral syndrome, or a lupus-like reaction.

There are conflicting data regarding the role of ATI in the development of delayed infusion reactions. In a clinical study of 40 patients with CD retreated with infliximab following a 2- to 4-year period without infliximab treatment, 10 patients (25%) experienced delayed infusion reactions and all were positive for ATI. This is in contrast to the ACCENT I results, in which none of the 11 delayed infusion reactions had detectable ATI and to the study by Baert and coworkers [2], which showed delayed infusion reactions to be unrelated to the development of ATI.

There are limited data regarding the actual pathogenetic mechanisms underlying an ATI-mediated infusion reaction (acute or delayed). Given the absence of an IgE response in most cases, the likely culprit is soluble immune complexes, which can trigger complement-mediated reactions and deposit in tissues (eg, serum sickness reaction). The formation of complexes is highly related to the amounts of both antigen (in this case infliximab) and antibody (ATIs). At antigen-antibody equivalence immune complexes form easily and are generally soluble. Increasing the antigen (antigen excess) reduces complex formation and may decrease reactions. This approach has not been tested in any specific trials to date but holds promise for altering the incidence of such reactions.

Shortened Duration of Response or Loss of Response to Infliximab

In both ACCENT I and ACCENT II, ATI status did not affect clinical response or remission overall at 1 year in patients receiving maintenance infusions. Of the patients who lost response on a 5 mg/kg maintenance regimen, increasing the dose to 10 mg/kg re-established response in 90%. Likewise, in

those patients on 10 mg/kg who lost response, 80% regained response when increased to 15 mg/kg. This is in contrast to two smaller studies that suggested a correlation between ATI status and decreased clinical response. Baert and colleagues [2] showed ATI concentration of 8 μg/mL or greater to be predictive of a shorter duration of response (35 versus 71 days among patients with ATI less than 8). No attempt to alter dose or interval was made in this study. Compared with ATI-negative patients, the 44 ATI-positive patients had a nonresponse rate of 52% (versus 14% in ATI-negative patients) and a shorter duration of response (28 versus 61 days) in the second study.

MEASURES TO MINIMIZE IMMUNOGENICITY

There are three general strategies to prevent the development of ATI and avoid the possible consequences, such as infusion reactions and decreased clinical response. First, infliximab should be given as more than a single-dose induction followed by scheduled maintenance regimen. Based on the best available evidence, this strategy is most protective against the formation of ATI. Second, all patients should receive an immunomodulator agent even if they did not respond to one previously. It is not clear which immunomodulator (azathioprine or 6-mercaptopurine versus methotrexate) is the optimal agent, nor is it clear what is the optimal dosing regimen. For example, in the case of methotrexate, is 7.5 mg orally an adequate weekly dose, or should it be given at 15 mg weekly as an injection? What is the lowest effective dose of azathioprine or 6-mercaptopurine? How long is the clinically relevant period of time for immunomodulator treatment before initiating infliximab? Can immunomodulator therapy be discontinued at some point during the maintenance phase without increasing the risk of ATI formation? A final optimization strategy is to pretreat with 200-mg intravenous hydrocortisone, but it is unclear whether this is sufficiently protective against ATI formation to serve as the only dose optimization strategy.

MANAGEMENT OF INFUSION REACTIONS

The management of infusion reactions should focus on alleviating the patient's symptoms, such as hypotension, chest pain, and dyspnea. A suggested infliximab infusion reaction treatment protocol, based on the experience at Mount Sinai, has been published previously and here is slightly modified. These modifications are based on continued clinical experience in treating and preventing infusion reactions. Importantly, the development of an infusion reaction does not preclude subsequent infliximab infusions. Pretreatment (prophylaxis) protocols were developed using previous desensitization protocols for 5-fluorouracil and vancomycin as templates (see Table 1).

Acute Infusion Reactions

Most patients with acute infusion reactions can be managed and retreated successfully. Symptoms usually resolve with adjustment of the infusion rate and administration of intravenous fluids; acetaminophen; antihistamines; and,

if needed, steroids. By slowing the rate of infusion, the opportunity for soluble immune complexes to form is greatly reduced. Epinephrine is indicated when wheezing and anaphylaxis is present. In the study by Cheifetz and coworkers [4], after receiving the appropriate medical prophylaxis, all of the patients who had mild or moderate acute infusion reactions tolerated retreatment and completed reinfusion with infliximab when clinically indicated. One patient with a moderate infusion reaction early in the study was not retreated because of the authors' limited experience at that time. Of the eight patients with severe infusion reactions, six tolerated reinfusion. Of the remaining two, one developed a second severe acute infusion reaction on reinfusion, and no further attempts were made. The other patient was not retreated. Although almost every patient tolerated retreatment, prophylaxis did not always prevent further infusion reactions. This underscores the fact that in cases of severe acute infusion reactions, the risks and benefits of reinfusion need to be weighed carefully.

Severe anaphylactic reactions are rare, but if they occur, the infusion should be stopped immediately, normal saline should be infused, and vital signs should be monitored closely. Epinephrine should be administered if indicated. Epinephrine and intravenous diphenhydramine should be given before steroids because of their faster onset of action. In these rare cases of anaphylaxis, the infusion should not be restarted. These patients may be eligible for desensitization [13] or treatment with a fully human anti–tumor necrosis factor-α antibody, such as adalimumab.

Delayed Infusion Reactions

Because delayed infusion reactions are much less common, there are far less data available on their treatment and prophylaxis. Although most physicians do not reinfuse infliximab after a documented delayed reaction, the authors propose that it is possible (see Table 1). Type III immune reactions occur when the antigen-antibody complexes are soluble. By increasing the dose of infliximab (antigen excess), one can shift the curve to the left and decrease the formation of soluble immune complexes. Antigen excess can be achieved by doubling the dose of infliximab from 5 mg/kg to 10 mg/kg or by decreasing the interval between the infusions. In the study by Cheifetz and coworkers [4], three patients experienced delayed infusion reactions. One patient's symptoms resolved spontaneously, and the patient was not retreated with infliximab. One patient was successfully retreated with infliximab without problems. Another patient was successfully retreated with infliximab with a concomitant 1-week course of oral diphenhydramine and acetaminophen. More recently, this has been changed to the use of a once-a-day nonsedating antihistamine (eg, cetirizine or fexofenadine) for 5 days before infusion. In some cases a methylprednisolone dose pack may be used to treat the delayed reactions.

SUMMARY

Infliximab therapy should be optimized to minimize immunogenicity, to prevent infusion reactions, and to maintain clinical response. Based on best available

evidence, strategies include minimizing the formation of ATI by administering infliximab as a multidose induction therapy followed by scheduled maintenance regimen, the use of concurrent immunomodulators, and possibly premedicating with steroids. Infusion reactions are common and they can be managed using specific protocols outlined in this article.

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Economics of the Use of Biologics in the Treatment of Inflammatory Bowel Disease

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Advances in the treatment of the inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), in the past decade has been characterized by the emergence of new monoclonal biologic therapies that have redefined the treatment of patients with these diseases. The unparalleled efficacy of these agents in patients with refractory IBD, as measured by clinical end points, endoscopic evidence of mucosal healing, and normalization of quality of life, has launched physicians and patients alike into the biologic world with a low likelihood of looking back.

This new world therapeutic approach to IBD has resulted in justifiable concerns over the economic impact of the use of the biologic therapies. With annual drug costs estimated to be in the tens of thousands of dollars, the enthusiasm over these agents' successes have been tempered by concerns of bankrupting the health care system. The cost of an illness, however, extends far beyond just the price of a particular medicine, but includes the costs of the health care services used and the indirect costs of decreased productivity at school and work, disability, and early retirement, for not only the patient, but also their caregivers.

This article reviews the economics of IBD; the expected clinical course of disease; and the impact of the new biologics on resource use and related costs, indirect costs, and patient quality of life. It discusses some of the existing cost analyses and their limitations. Understanding these contributing issues to the economics of IBD is important for not only heath care professionals and their patients, but also for those whose professions involve decisions based on the cost of care for individuals with disease and for the health care system.

THE ECONOMICS OF INFLAMMATORY BOWEL DISEASES

The initial studies on IBD economics in the United States were conducted in the late 1980s, when the health care landscape was much different than today.

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In the first [1] of two companion studies [1,2] in the *Journal of Clinical Gastroenterology*, the authors applied an analysis of IBD practice patterns and their estimated costs to an algorithm to estimate the diseases' overall impact on costs. The medical decision cost algorithm was derived by the application of data from an extensive literature review to 100 hypothetical CD and 100 hypothetical UC patients. Their estimates of average annual costs were $6561 for CD and $1488 for UC, with annual United States cost estimates of $1 to $1.2 billion (CD) and $400,000 to $600,000 (UC). The authors' group subsequently updated the CD figures to 1996 dollars in a recent review to over $9000 per patient, and $1.7 billion United States costs [3]. Surgery and hospitalizations accounted for 80% of CD costs, and 47% of UC costs.

The second study [2] looked at medical claims submitted to a large commercial insurer (CIGNA Corporation) from 1988 to 1989. Overall, CD charges exceeded $25 million, with 2% of CD patients accounting for 29% of charges and 34% of dollars paid. Overall UC charges exceeded $3 million, with the top 2% patients accounting for 36% of total charges and 39% of dollars paid. Regression analysis predicted that a new medication that doubled medication costs but, presumably because of its efficacy, decreased use of other health care services by 20%, would decrease overall CD costs by 12.9% and UC costs by 10.9%.

This disproportionate use of health care dollars was echoed in a subsequent database study of a large United States health insurers' 1994 medical and pharmacy claims for CD [4]. Patients were stratified into three groups, as defined by disease severity. Group 1 patients had filed an inpatient hospitalization claim with a primary or secondary diagnosis of CD. Group 2 had required "aggressive" medical therapy, defined as the use of chronic moderate to high-dose glucocorticoids or immunosuppressives. The remaining patients comprised Group 3.

There was a clear association between disease severity and charges, with group 1 patients accruing annual charges three-times higher than group 2, and six-times higher than group 3 (Table 1). Hospitalizations accounted for over 75% of group 1 charges, and over 50% of the overall charges accrued by all patients. A separate analysis of patients with fistulizing CD revealed that hospitalizations accounted for over 70% of overall charges. Overall, 25% of patients accounted for 80% of the total charges.

Table 1
Annual charges for Crohn's patients, according to severity of disease as measured by need for hospitalization or aggressive medical therapy

Patient group	Hospitalized	Aggressive therapy	All others	All patients
% of patients	19	5	76	100
Average annual charges	$ 37,135	$ 10,033	$ 6277	$ 12,417
Median annual charges	$ 21,671	$ 5581	$ 2703	$ 3668

Values shown are per patient annually.

Data from Feagan BG, Vreeland MG, Larson LR, et al. Annual cost of care for Crohn's disease: a payor perspective. Am J Gastroenterol 2000;95:1955–60.

The use of hospital resources and the associated costs in CD was subsequently studied by the authors' group at the University of Chicago in the mid-to-late 1990s [5]. Surgical admission accounted for the largest proportion of hospitalizations (57%) and the largest proportion of costs (nearly 40%). Although surgeons' charges accounted for only 18% of the number of charges, they were 56% of the total dollars charged. Overall, surgery accounted for 57% of admissions, 40% of costs, and nearly 75% of overall charges and revenues (Fig. 1). Pharmacy costs accounted for nearly one fifth of overall costs, with total parenteral nutrition–related costs responsible for 63% of total pharmacy costs, although it was used in only 27% of the hospitalizations. Medical admissions were three-times longer in patients requiring total parenteral nutrition, at nearly four-times the cost. It is noteworthy that even in the Scandinavian health care model, which differs greatly from that of the United States', hospitalizations were found to account for 58% of direct costs, nearly identical to the North American findings [6].

The story was similar across the border in Manitoba, Canada. In one hospital's 362 IBD hospitalizations from 1994 and 1995, surgery accounted for nearly 50% of admissions, 58% of hospital days, and 61% of costs [7]. Total parenteral nutrition was used in 9.5% of cases accounting for 27% of overall costs. The mean length of stay for the medical IBD patients who received total parenteral nutrition was over four-times longer at approximately five-times the mean cost than for those who did not receive total parenteral nutrition.

Studies in the United Kingdom have echoed similar sentiments to those across the Atlantic [8]. In a 6-month study of 307 cases of ulcerative (or indeterminate) colitis and 172 cases of CD, inpatient services were required by 14% of patients, but accounted for 49% of total secondary care costs. Drug costs

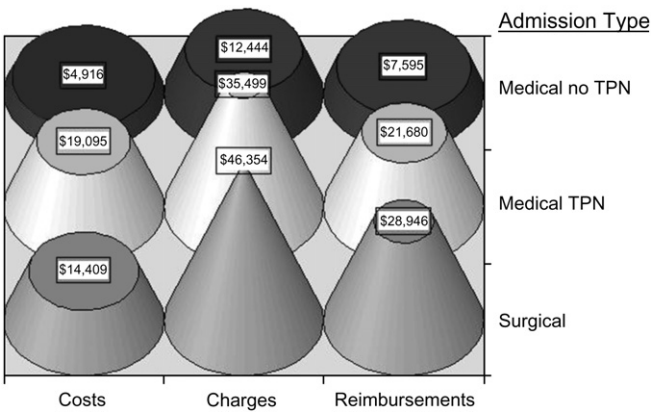

Fig. 1. Average costs, charges, and reimbursements per Crohn's disease hospitalization over a 1-year period at the University of Chicago. TPN, total parenteral nutrition. (*Data from* Cohen RD, Larson LR, Roth JR, et al. The cost of hospitalizations in Crohn's disease. Am J Gastroenterol 2000;95:524–30.)

were low, accounting for less than a quarter of total costs. Individual patient costs ranged from £73 to £33,254 per 6 months. Mean (95% CI) 6-month costs per patient were £1256 (range £988–£1721) for colitis and £1652 (£1221–£2239) for CD. Hospitalization, disease severity grade, and disease extent correlated positively with cost of illness. Disease relapse was associated with a twofold to threefold increase in costs for nonhospitalized cases and a 20-fold increase in costs for hospitalized cases, as compared with patients with quiescent disease. Survey data suggested average 6-month costs were <£30 per patient for primary care visits (both diseases) and median loss of earnings were £239 for colitis and £299 for CD.

Studies of IBD drug use in Sweden in the prebiologic era revealed that CD patients were predominately receiving aminosalicylates and nutritional supplements, with an annual rate of 0.55 million daily doses per million population [9]. For UC patients, drug exposure was 0.61 million daily doses per million per year. Overall, the annual average cost for IBD drugs was $7 million (United States dollars).

CLINICAL COURSE OF INFLAMMATORY BOWEL DISEASES

Economic determinations of the cost of disease must include an understanding of the anticipated clinical course of disease, to allow for future projections for individual costs; group costs (ie, within a particular insurance plan or plans); and society costs (ie, impact on national allocation of health care resources, anticipating disability claims, calculating the impact on productivity, and so forth).

There are a few characteristics about IBD that make these determinations especially important. First, the typical age on onset for IBD is much lower than most other diseases that clinicians treat. Many patients are first diagnosed in the second or third decade of life, with symptoms often starting years prior [10]. Second, the average life expectancy for patients with UC is the same as for healthy adults [11]; it may be the same or slightly reduced for patients with CD [12,13]. Third, epidemiologic studies have historically shown that these diseases are most prevalent in industrialized first world nations, northern climates, and some have suggested preponderance in wealthier patients [14,15]. The result from this "recipe" is a potential for a considerable economic impact, because patients potentially use health care resources for scores of years, and the costs to the business world and the economy are higher when their productivity falls.

One of the most comprehensive studies of the course of disease was a Markov model by a consortium of American and Canadian investigators who evaluated the clinical course of disease in CD patients from 1970 through 1993 in Olmstead County, Minnesota [16]. Seven possible disease severity states were defined by the use of various medical or surgical therapies, with the likelihood of transition between the different Markov models determining the proposed chronologic course for each patient (Table 2). Charge data were compared for each patient with 10 age- and sex-matched controls who did not

Table 2
Crohn's disease clinical course: disease severity states used in Markov model

Disease severity state	Medications and outcomes
Remission	No medication, other than antidiarrheals
Mild disease	Therapy with first-line agents
	5-ASA compounds[a]
	Antibiotics[b]
	Topical therapy
Severe disease, drug-responsive	Improvement with
	Oral corticosteroids
	Immunosuppressives[c]
Severe disease, drug-dependent	Improvement with at least 6 mo of
	Oral corticosteroids
	Immunosuppressives[c]
Severe disease, drug-refractory	No improvement after
	2 mo of corticosteroids
	6 mo of immunosuppressives[c]
Surgery	Inpatient hospitalization for Crohn's surgery plus
	6 wk posthospitalization convalescence
Postsurgical remission	No treatment for Crohn's after Crohn's surgery
Death	Death from any cause

[a]5-ASA agents: mesalamine, sulfasalazine, olsalazine.
[b]Antibiotic agents: metronidazole or ciprofloxacin.
[c]Immunosuppressive agents: 6-meracaptopurine, azathioprine, methotrexate, cyclosporin A.
Adapted from Silverstein MD, Loftus EV, Sandborn WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology 1999;117:49–57.

have CD, and was expressed in 1995 United States dollars. The highest monthly charges were seen among patients in the "surgery" state ($7438); next came the "severe, drug-responsive state" ($619).

The model's assumptions were then applied to a hypothetical Crohn's patient, first diagnosed at age 28, to calculate projected clinical course and costs over that patient's expected 46 additional years of life. Most of the time was expected to be spent in remission: 41% of the time in postsurgical remission, and 24% in medically induced remission. Another 27% of the time was anticipated to be spent in a mild disease state, leaving only 8% of the time in a more-active disease state. Projected lifetime costs were nearly $40,000 in charges, the largest proportion because of surgery (44%).

It is important to note that the study's time frame came before the widespread use of branded mesalamines, immunosuppressants, and the advent of biologic therapies, so the economic calculations are of questionable value today [17]. The authors did anticipate some of these shortcomings, and included a sensitivity analysis of the impact on overall lifetime costs if the mesalamines and immunosuppressant were factored into the equation. The analysis suggested that a dollar increase in the price of minimally effective aminosalicylates increased projected lifetime costs by nearly 10-times the dollar amount than results from a similar $1 increase in the price of the more effective

immunosuppressives. Infliximab and other biologic therapies were not included; nor were such agents as budesonide, which has supplanted the use of prednisone in many patients.

Another weakness of their dataset is that the practice patterns in the treatment of IBD have radically changed since the 1970s, and even the 1990s. These include the previously mentioned medication changes; the practice of using medical therapies in a purely prophylactic mode postoperatively [18–23]; the shift away from the inpatient toward outpatient care for many patients; decreased reliance on total parenteral nutrition as a therapeutic and supportive therapy; and the emergence of bowel-sparing stricturoplasties, which no longer remove the diseased segments of bowel. It is difficult to calculate the true impact of each of these "high-ticket" items on the expected clinical course and costs.

INDIRECT COSTS AND DISABILITY

The indirect costs of disease are those costs that are calculated as a result of the impact of disease on areas of a patient's life that are not readily assigned a true dollar amount, or those tangible costs that result from disease impact on a patient's life. Examples include the economic impact of early retirement, disability, and decreased work or school productivity. Other items might be lost earning potential because of missed promotion, choice of career or location, or other limitations either externally or self-imposed as a result of the illness. Indirect costs are not only accrued by the patient, but also by their caregivers, friends, and even those who must be enlisted or hired to perform functions that the patient cannot do as a result of disease. Although rarely discussed and typically omitted from economic analyses, indirect costs are arguably the largest and most important part of the financial equation. When multiplied per patient per year, the impact on businesses, employers, insurers, and public policy may be staggering.

The most comprehensive study of indirect costs in IBD patients to date is from the early to mid-1990s in Sweden. Indirect costs were estimated to account for 68% of overall costs, primarily because of sick leave and early retirement [6]. Sick leave was more common in CD patients (0.39 per prevalent patient) than UC patients (0.09), with a mean duration of 45 days. The incidence of early retirement (1994 data) was 2.5 per 100,000, with an average duration of 14 years, with 1% of CD patients and 0.03% of UC patients receiving early pensions.

The impact of juvenile-onset of IBD on education and employment was the focus of a Scottish study, with 60% of CD patients and 50% of UC patients reporting an adverse impact on their education; work-time losses secondary to IBD was claimed by 70% and 74%, respectively [24]. In West Germany, disproportionately high disability rates were reported in female IBD patients and in those holding white-collar jobs [25]. Annual work disability was estimated to be 5% to 10% among IBD patients in the Hay's studies [1,2], although they relied primarily on Scandinavian studies to derive these rates.

Baseline employment and disability data from the ACCENT I (international trial of infliximab in luminal CD) [26] was sobering; full- and part-time employment rates were only 48% and 13%, respectively, with 39% of patients unemployed and 25% receiving disability compensation [27]. Of the 225 unemployed patients, only 14% stated that they felt well enough to work if a job were available. There was a higher likelihood of unemployment in patients of younger age, female gender, shorter disease duration, and with a prior bowel resection. Similarly, younger age and female gender also predicted a higher likelihood of not being employed full-time, and prior bowel resection predicted a higher likelihood of receiving disability compensation.

Subsequent employment and disability data from this trial revealed encouraging trends linking clinical and quality of life improvement to gains in employment [28]. At baseline, 38.4% of the patients reported themselves as unemployed. Among these patients, 31% of those patients who achieved Crohn's Disease Activity Index (CDAI) remission (CDAI $<$ 150) at week 54 were employed, compared with 16% who were not in CDAI remission at week 54 ($P < .05$) (Fig. 2). Gains were also noted in achieving full-time employment; the proportion of patients who became employed full time at week 54 was higher among patients in remission (29%) versus those who were not in remission (18%). The number of work hours lost during the course of the study was also significantly lower among those who spent more time in CDAI remission.

The impact of fistulous CD on disability rates and unemployment was also surveyed in the ACCENT II study (international trial of infliximab in fistulous CD) [29,30]. Among the 306 patients (median duration of CD 11.5 years,

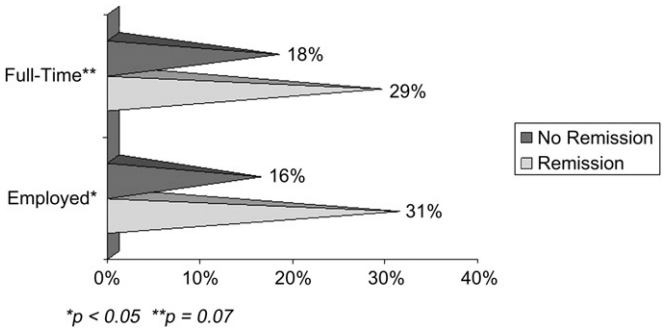

Fig. 2. Gain in employment was related to remission status at week 54 among 162 Crohn's disease patients who were unemployed at the beginning of the ACCENT I trial (*employed*). Gain in full-time employment was related to remission status at week 54 among 162 Crohn's disease patients who were not employed full-time or were unemployed at the beginning of the ACCENT I trial (*full-time*). $*P < .05$. $**P = .07$. (*Data from* Lichtenstein GR, Yan S, Bala M, et al. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. Am J Gastroenterol 2004;99:91–6.)

55.9% had previous bowel resections), baseline employment data were as follows: 55% full time, 33% unemployed, and 11% part time. Disability compensation was received by 18%. Not having full-time employment was associated with number of fistulas, having prior gastrointestinal surgeries, higher CDAI, and female gender. Receiving disability was associated with having greater number of fistulas and having prior bowel resection.

THE IMPACT OF THERAPIES ON RESOURCE USE

The advances in medical care over the past two decades have in part been reflected in the studies discussed previously. The introduction of the non–sulfur-containing aminosalicylates, expansion of the role of the immunosuppressants, and the dawn of the biologics has raised the potential of dramatically changing the economic landscape in IBD. The substantial increase in medication costs anticipated from the use of these agents must be balanced against their potential for decreasing use of health care, and their associated costs, to estimate truly their overall economic impact.

The authors' group studied the influence of infliximab on use of health care services in CD at the Inflammatory Bowel Disease Center at the University of Chicago [31]. This analysis compared the rate of use of services in CD patients before and after their initial infliximab infusion. Areas studied included hospitalizations, hospitalized days, surgeries, emergency room and outpatient visits, endoscopies, and radiographs. Patients decreased their use of surgeries by 38%, gastrointestinal surgeries by 18%, emergency room visits by 66%, outpatient clinics by 16%, gastrointestinal outpatient visits by 20%, endoscopies by 43%, and radiographs by 12%. Fistulizing CD patients experienced a 59% decrease in hospitalizations, whereas hospitalized days trended toward 9% decrease among all CD patients.

This study was subsequently expanded to a 3-year controlled analysis, with a comparison of use up to 3 years before and 3 years after an initial infliximab infusion, and compared with infliximab-naive controls [32]. Among the patients who received infliximab, decreases were seen in hospitalizations (37%); outpatient visits (gastrointestinal 41%, rheumatology 54%, total 33%); endoscopies (52%); and radiographs (58%). When compared with control patients (many of whom were not ill), the infliximab patients had lower use rates of the emergency room (372%); endoscopies (52%); radiographs (147%); and outpatient visits (gastrointestinal 10%, total 22%).

A similar study was subsequently performed by British investigators who audited the charts of 205 patients with moderate-to-severe CD, comparing health care use in the 6-months before and following initial infliximab infusion. There was a dramatic fall in hospitalized days (1435 versus 342) and fewer surgeries, examinations under anesthesia, and diagnostic procedures [33]. Unlike the University of Chicago data, there was no change in outpatient visits. It remains to be seen whether these trends continue over time.

The impact of infliximab on health care resource use was also studied in the ACCENT I trial [26,28]. Hospitalization and surgery rates decreased as the

percentage of time patients were in CDAI remission increased ($P < .01$ and $P < .05$, respectively). The hospitalization rate for patients in CDAI remission less than 25% of the time was greater than three-times that of patients in CDAI remission for greater than 75% of the time. The surgery rate for those in remission less than 25% of the time was greater than five times the rate of those in remission at least 75% of the time. The average number of days hospitalized was also significantly lower among those who spent more time in CDAI remission.

Differences within the ACCENT I groups were even seen between those patients receiving scheduled maintenance infusions (automatically every 8 weeks) than those receiving episodic therapy (treatment on flare) [34]. Those receiving scheduled maintenance infliximab had lower numbers of CD–related hospitalizations (Fig. 3) and fewer CD–related surgeries (3 of 100 patients versus 7 of 100 patients $P = .01$) than in the episodic treatment strategy group.

The impact of infliximab was also studied in the ACCENT II trial [29]. The 192 patients who responded to an initial three-infusion course of infliximab were subsequently randomized to infusions of infliximab, 5 mg/kg, (or placebo) every 8 weeks. Fewer patients who received infliximab maintenance were hospitalized (7.3% versus 18.2%; $P < .05$) and had a longer time to first hospitalization [35]. They also had fewer mean hospitalization days (0.5 versus 2.5 days; $P < .05$), fewer mean number of hospitalizations (per 100 patients) (11 versus 31; $P < .05$), fewer "all surgeries and procedures" (65 versus 126; $P < .05$), fewer "inpatient surgeries and procedures" (7 versus 41; $P < .01$),

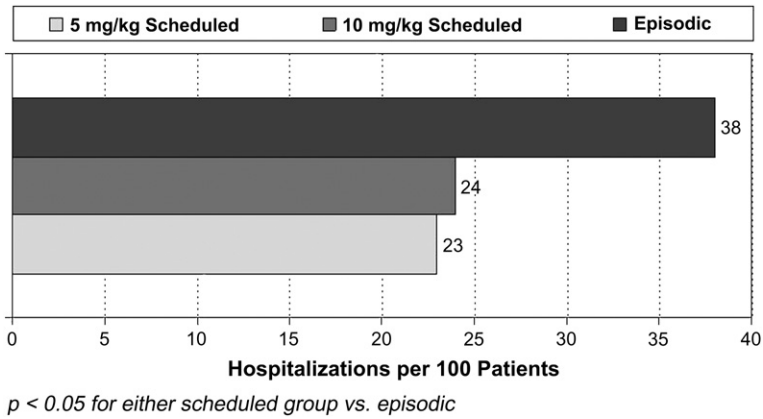

Fig. 3. The number of hospitalizations per 100 Crohn's disease patients treated with scheduled maintenance therapy with infliximab, 5 mg or 10 mg/kg, versus those treated with episodic infliximab infusions in the ACCENT I trial. $P < .05$ for either scheduled group versus episodic. (*Data from* Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402–13.)

and fewer major surgeries (2 versus 11; $P < .05$), compared with those who received placebo.

Similar results were seen for the entire group of randomized patients, with those subsequently receiving infliximab maintenance less likely to be hospitalized (8.6% versus 18.9%; $P < .05$), with fewer mean numbers (per 100 patients) of hospitalizations (14 versus 31; $P < .05$), all surgeries and procedures (60 versus 118; $P < .01$), inpatient surgeries and procedures (10 versus 45; $P < .001$), and major surgeries (2 versus 13; $P < .05$), compared with those who received placebo maintenance (Fig. 4).

THE IMPACT OF THERAPIES ON COSTS

The research studies to date suggest a substantial impact on research use by infliximab, a trend that should continue with the introduction of other biologic therapies into the field. There is obvious cost savings if valuable medical resources are saved; yet, these therapies at first glance seem to be far more expensive than traditional therapies. The question that arises is whether these therapies can be cost-neutral, or even cost-saving, in the management of IBD. This scenario was the topic of a regression analysis of the Hay's [1,2] data from the late 1980s. Their model suggested that a new therapy that doubled the medication cost, but decreased the use of health care resources by 20%, would translate into a total direct cost savings of nearly 13% in CD and 11% in UC.

The cost implications of infliximab were analyzed in some of the previously mentioned studies of health care use. In the University of Chicago's 3-year study, median charges increased in the patients who received infliximab; over half of their charges were because of the drug [32]. The Oxford Group's

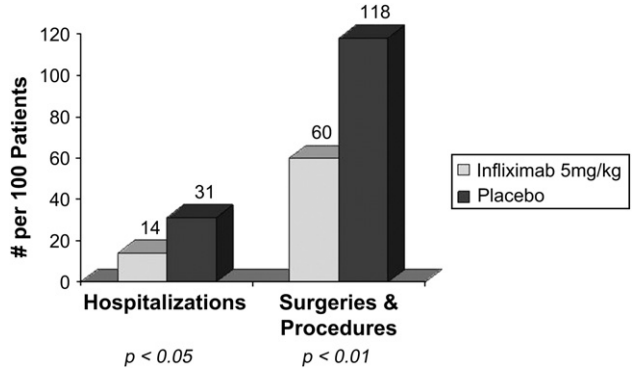

Fig. 4. Number of hospitalizations ($P < .05$) and surgeries or procedures ($P < .01$) per 100 patients for all randomized patients in the ACCENT II trial of infliximab therapy in fistulous Crohn's disease. (*Data from* Lichtenstein GR, Yan S, Bala M, et al. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005;128:862–9.)

data suggested an overall cost savings of £138 (roughly $230 at current exchange rates) per infliximab patient [33].

Many of the cost-effectiveness and utility analyses suggested that infliximab use was associated with rather high incremental cost per quality-adjusted life-year; however, it is important to realize that these analyses were often based on flawed assumptions, left out critical calculations from their data, or were purely theoretical and not done within the confines of a clinical study [36–43].

One common theme in many of these studies, or their editorials, is the difficulty in applying standard cost-effectiveness measurements (eg, quality adjusted life-years) to such diseases as IBD, which have a low mortality but high morbidity, and because of the relative young age of onset, a potential for considerable medical costs. These studies also rely on quality-of-life data to gauge the overall impact of a therapy, as compared with other standards. As discussed in the next section, quality-of-life scales may not be sensitive enough to differentiate between two effective therapies, even those that are disease specific. Another chronic problem with these studies is the nearly universal exclusion of indirect cost data from the analysis, or reliance on vague estimates of such costs [43].

In the United States, studies on infliximab costs have been confounded by the wide fluctuation of markups that are seen throughout the health care delivery system. Because infliximab is an infusible agent, the inclusion of the middle-man infusion center, physician office, surgical center, or even inpatient hospitalization can result in tremendous variations in costs passed onto the patient and health care system. These changes can result in drug costs being elevated threefold to fivefold in some instances. As a result, the infusible agents are far more likely to have their costs escalated than injectables. Because technologic advances are leading somewhat away from infusible biologics in IBD, more accurate cost estimates can likely be done for the newer wave of injectable therapies.

QUALITY OF LIFE

The formalized assessment of quality-of-life outcomes in patients with IBD is an entire topic of its own. The importance of quality of life is reflected in the inclusion of one or more health-related quality-of-life (HRQOL) scales in most modern IBD clinical trials. This may be because of some of the unique characteristics of these disease, which are often diagnosed at a relatively young age; follow a chronic, relapsing course; but usually have a normal life expectancy. Patients with IBD need to balance the impact of their disease with the other demands on their life and lifestyle.

Quality of life in Crohn's patients has been shown to be worse than in patients with UC [43,44], worse than in healthy controls [44,45], and directly related to disease activity [44–46]. UC patients also show greater impairment than HMO controls [47], with a direct relationship between quality of life and disease activity [45,48]. Patients are most concerned with the need for an ostomy bag, the effects of medications, fear of surgery, and the uncertain

nature of their disease [49]. Because of the unique issues inherent in having a stoma, such as body image and sexuality, emotional and social functioning components of quality-of-life scales are often lower than the physical components [47,50].

Most of the new biologic agents have been studied in patients with moderate-to-severe CD, a patient group one expects to have poor quality-of-life responses. This was reflected in the baseline study of the ACCENT I CD population [27]. In these patients with a mean baseline CDAI score of 297, the baseline SF-36 Physical Component Score was 34 and Mental Component Score was 39, which were 1.5 and 1 standard deviation lower than the general United States population. Achieving remission in these patients was associated with significantly higher Physical Component Score and Mental Component Score than in patients not in remission ($P < .0001$) [28].

Closer analysis of the HRQOL data from the ACCENT I study reveals that the total Inflammatory Bowel Disease Questionnaire (IBDQ) score at weeks 10, 30, and 54 was significantly greater ($P < .05$) in both the three-dose induction (at week 10) and the maintenance groups at week 30 and 54 [51]. Because all patients initially received an initial infusion of active drug, it is not surprising that all treatment groups had a significant increase in IBDQ score of 40 points within the first 2 weeks. At week 10, the three-dose induction group had higher IBDQ scores than the single-dose group (37.8 higher than baseline versus 28.9 higher than baseline, respectively). This trend continued in both of the maintenance groups the remainder of the trial for all four dimensions of the IBDQ. The mean change in IBDQ scores in both the 5 mg/kg group (22.1, $P < .05$) and the 10 mg/kg group (30.2, $P < .001$) were greater than in the single-dose group (8.9). The SF-36 scores also rose from baseline in all three groups at weeks 10, 30, and 54. The improvement in SF-36 scores was greatest in the physical aspects of health as compared with the psychologic measures, with greater changes in the Physical Component Score seen in the 5 mg/kg (6.1, $P < .05$) and 10 mg/kg maintenance group (7.2, $P < .01$) than in the single-dose group (2.5). The 10 mg/kg group also was more likely than the 5 mg/kg group to show significant improvement in individual SF-36 scales when compared with the episodic treatment group. Correlation scores between the IBDQ and CDAI were highly significant at week 54, with a less-direct relationship between the SF-36 and the CDAI.

The initial large placebo-controlled trial of infliximab in CD also showed substantial improvement in HRQOL in patients receiving the active therapy [52,53]. There was a significantly greater improvement with infliximab than placebo in overall IBDQ score ($P < .001$) and in all four IBDQ dimensions: (1) bowel ($P = .007$); (2) social ($P = .002$); (3) emotional ($P < .001$); and (4) systemic ($P < .001$). More infliximab-treated patients reported having normal or near-normal frequency of bowel movements ($P < .001$); full or a lot of energy ($P = .019$); no or hardly any difficulty doing leisure or sports activities ($P = .011$); and being extremely or very satisfied with their personal life ($P = .046$). Differences were also seen in responses regarding fatigue,

frustration, ability to work, general well-being, depression, anxiety, and anger resulting from bowel problems.

Other smaller quality-of-life studies have shown similar improvements with infliximab. A multicenter observational Dutch study of 65 patients receiving a single infusion of infliximab, 5 mg/kg, for luminal CD showed improvement at week 4 in the mean total and dimensional IBDQ scores ($P < .001$) [54]. Fistula patients received three infusions at 5 mg/kg, with week 6 improvement of all scores from baseline ($P < .05$). In both disease types, improvement in the total IBDQ correlated with the improvement in CDAI. A Spanish prospective study in 25 CD patients with multiple draining abdominal or perianal fistulas revealed improvement in HRQOL after three infusions of infliximab (5 mg/kg; weeks 0, 2, 6) [55]. Improvements in the Physical Component Score domain of the SF-36 were noted at weeks 4 and 10 ($P < .05$), with an increase in the IBDQ noted at week 4 ($P < .01$), with the exception of the social functioning subscale.

Quality-of-life analyses with other biologic therapies have also had encouraging results, with dramatic improvements in generic or disease-specific scores with a variety of therapies and in different medication classes. Many of the newer monoclonal antibodies targeting tumor necrosis factor-α are including formalized HRQOL analyses in their clinical trials [56].

The anti-integrin class of antibodies and molecules has also examined HRQOL outcomes in clinical trials. UC patients who received the humanized monoclonal antibody to the $\alpha_4\beta_7$ integrin mLN-02 had a 30- to 40-point improvement in the IBDQ scores within 4 to 6 weeks, nearly twice as high as that seen with placebo ($P = .02–.03$, respectively) [57]. Improvements in the IBDQ scores were also noted in CD patients treated with natalizumab, a humanized monoclonal antibody to the $\alpha_4\beta_1$ integrin [58]. Patients who received just one infusion had significantly greater improvements in the CDAI than did those who received placebo (increase of 25 versus 15 points, $P = .008$), whereas those who received a second infusion maintained that improved quality-of-life scoring (3 mg/kg: $P = .021$; 6 mg/kg $P = .14$ versus placebo).

The vast improvement in quality-of-life scores to "normal" with the biologic agents, along with comments from patients who received infliximab stating that the lifestyle they previously thought was remission has now been redefined as even better than previously thought attainable, has raised the question of the need for a more sensitive quality-of-life scale to differentiate these states. This also has dramatic implications on cost-effectiveness models in IBD; a survival-based end point is not appropriate in diseases with high morbidity but low mortality. Quality of life–based outcomes have been advocated as a potential replacement for a survival end point [43,59]. The term "quality-adjusted life-year" itself may need to be refined to reflect the incremental gains in quality of life previously not believed possible, and not detected by older HRQOL scales.

SUMMARY

The introduction of the biologic therapies into the therapeutic regimen for IBD, coupled with the vast changes seen in health care delivery within the past

decade, have turned previous economic assumptions and models on their head, and opened up a new opportunity to redefine what is truly the cost of a disease, and of its' interventions. Pundits and pencil-pushers are quick to point to the high drug cost as a threat to the economic stability of the health care system, without first doing a carefully planned, balanced analysis of the overall impact that such a therapy will make on the entire cost-structure of the system. This is also true outside of the United States, where those who must budget and pay for the therapies do not pay for the use of health care services, and simply enter the drug costs on an accountant's debit sheet.

Such analyses are complicated, because they must calculate the impact that such therapies have on the direct costs of health care and the indirect costs for both the patient and their families or health care support system. Realizing what impact these therapies might have on altering the natural history of these previously relentless chronic debilitating conditions, and redefining how normal quality of life can actually get on these therapies, should be the focus of future studies as clinicians try to calculate truly whether these agents are cost savings for society overall.

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Treatment of Immune-Mediated Extraintestinal Manifestations of Inflammatory Bowel Disease with Infliximab

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Extraintestinal manifestations (EIM) associated with the chronic inflammatory bowel diseases (IBD) ulcerative colitis and Crohn's disease (CD) have a negative impact on morbidity and even mortality in a significant percentage of patients who have IBD. For most EIM, exacerbation and resolution parallel the activity of bowel inflammation. Some EIM, however, such as axial arthritis, pyoderma gangrenosum, and primary sclerosing cholangitis, may run a clinical course independent of the IBD activity. For this challenging patient population, the introduction into clinical practice of targeted immunomodulatory agents provides important new therapeutic options. The chimeric (mouse/human) anti–tumor necrosis factor (TNF) IgG1 monoclonal antibody infliximab is highly effective for the induction and maintenance of remission in moderate-to-severe CD and ulcerative colitis resistant to conventional therapies [1–5]. Important and unique properties of infliximab include fistula closure, mucosal healing, and steroid sparing. Additionally, infliximab has emerged as an effective treatment for immune-mediated EIM often refractory to other interventions (Table 1). This article reviews experiences with infliximab to treat immune-mediated EIM of IBD.

EIM occur in approximately 25% of patients who have IBD [6–9] and can be divided into three distinct classes [10,11]. The first class comprises immune-mediated diseases of the joints, skin, and eyes that usually but not invariably correlate with intestinal inflammatory disease activity. The prevalence of immune-mediated EIM in patients who have IBD has been reported to range from 6.2% to 36% [10,12,13]. The second category includes complications

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Table 1
Level of evidence in favor of infliximab for the treatment of various extraintestinal manifestations of inflammatory bowel disease

Extraintestinal manifestation	Retrospective case data	Prospective open-label data	Randomized controlled data
Ankylosing spondylitis	yes	yes	yes
Erythema nodosum	yes	no	no
Metastatic cutaneous Crohn's disease	yes	no	no
Peripheral arthropathy	yes	yes	yes
Psoriasis	yes	yes	yes
Pyoderma gangrenosum	yes	yes	yes
Uveitis	yes	yes	no
Primary sclerosing cholangitis	yes/no	no	no
Autoimmune hepatitis	no[a]	no	no

[a]Exacerbations reported.

that are directly predisposed by chronic IBD, such as obstructive uropathy, malabsorption, nephrolithiasis, and cholethiasis. The third category consists of manifestations that cannot be classified into either of the first two categories, such as amyloidosis.

IMMUNE-MEDIATED JOINT EXTRAINTESTINAL MANIFESTATIONS

IBD-associated arthropathy is a form of spondyloarthropathy (SpA), a group of interrelated autoimmune joint disorders that also includes ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, and undifferentiated SpA. Peripheral arthropathy occurs in 10% to 20% of patients who have IBD, typically presents in large joints, and is further characterized as pauciarticular, asymmetrical, and migratory [11,14]. IBD-related peripheral arthropathy has a recurring nature, often flaring upon relapse of bowel disease. Consequently, medical or surgical treatment of IBD usually is associated with improvement in peripheral arthritis. In contrast, the clinical course of axial arthropathy is frequently independent of the IBD state. IBD-related axial arthropathy includes sacroiliitis, observed radiographically in 20% to 25% of patients, and both HLA-B27–positive and –negative AS, with a prevalence of 3% to 10% [14]. First-line agents for the treatment of mild-to-moderate joint EIM consist of acetaminophen, sulfasalazine, and mesalamine [15]. Second-line treatment agents include corticosteroids, methotrexate, and, with great caution in IBD, nonsteroidal anti-inflammatory drugs.

Anti-TNF therapy for IBD has been influenced by its successful application in rheumatoid arthritis (RA). Both infliximab and the fully human, TNF-neutralizing IgG1 antibody adalimumab ameliorate symptoms in RA [16–18]. Of

note, adalimumab recently has been shown to induce remission in moderate-to-severe CD [19]. In addition to antibody-mediated therapy, the soluble TNF receptor etanercept is an effective therapy for RA [20] but, interestingly, not for CD [21]. This key difference in etanercept susceptibility may highlight important differences in TNF biology in the two diseases, which are beyond the scope of this article [22]. Importantly, TNF inhibitors in RA have been demonstrated to stop the progression of erosive joint disease and prevent long-term disability, thus altering the natural course of this chronic inflammatory disease [23]. The coincidence of RA and IBD has been reported; more importantly, the experience with TNF inhibition in RA provides important impetus for consideration of this approach in the more common inflammatory joint manifestations in IBD [24,25].

Of the immune-mediated EIM, infliximab therapy has been most thoroughly investigated in joint disorders, in part because of its therapeutic origins in RA [17]. Various case studies suggesting a therapeutic role for TNF inhibition in IBD-associated joint conditions have been reported since the completion of colitis-specific trials of infliximab [26–28]. One such early report by Van den Bosch and colleagues [28] described infliximab-mediated improvement in four patients who had CD-associated SpA (peripheral, n = 3; axial, n = 2) characterized by symptom resolution, decreased joint swelling, and suppressed C-reactive protein serum levels [28]. They then expanded their initial findings by testing the efficacy of infliximab for the specific treatment of active SpA, first in an open pilot study [29] and then in a randomized, double-blind trial of 40 total patients who had multiple subtypes of SpA [30]. Following a loading-dose regimen of infliximab (5 mg/kg at 0, 2, and 6 weeks), they observed statistically significant differences in disease-specific clinical assessments (patient and physician assessments of global disease activity), joint findings, and proinflammatory serum markers (erythrocyte sedimentation rate and C-reactive protein) in infliximab-treated and placebo-treated patients [30]. Patients' symptoms improved rapidly after the first infusion and remained in remission through the end of the trial, approximately 6 weeks after the last of three infusions. Efficacy in SpA has been suggested in open-label maintenance analyses of infliximab over 1 year [31,32].

Other research endeavors have focused specifically on the treatment of AS through TNF inhibition [33]. Braun and colleagues [34] first demonstrated that infliximab ameliorated active AS in an open-label study. An independent 6-month open-label study of infliximab involving 48 patients who had active AS corroborated the first study [35]. In a pivotal study, infliximab was superior to placebo for the treatment of active AS in a multicenter, double-blind, randomized, controlled trial [36]. The investigators observed that 18 of 34 infliximab-treated patients had at least 50% improvement, as defined by the Bath Ankylosing Spondylitis Disease Activity Index, compared with 3 of 35 placebo-treated patients at 12 weeks. Braun and colleagues [37] extended this initial study for up 2 years, with patients receiving 5 mg/kg of infliximab every 6 weeks. They reported that 30 of 52 treated patients had a 50% or greater

decrease in their baseline disease activity at week 102, with no observed difference in the long-term versus short-term side-effect profile of infliximab.

The aforementioned SpA and AS trials did not specifically investigate patients who had IBD with joint EIM. In contrast, two independent reports by Herfarth and colleagues [38] and Generini and colleagues [39] described infliximab-mediated improvement of rheumatologic manifestations in CD. Herfarth and colleagues [38] identified 59 of 153 patients who had CD participating in a multicenter, open-label infliximab trial who also complained of arthritis or arthralgias. Thirty-six of the 59 patients had at least partial resolution of joint symptoms at 12 weeks after receiving the infliximab loading-dose regimen, and 27 of the 59 patients were symptom free. Concurrently, all 59 patients had a decrease in the CD activity index. Generini and colleagues [39] studied 24 patients who had either active or inactive CD and SpA who received repeated infliximab infusions over a 12- to 18-month period. They observed that infliximab suppressed axial and peripheral arthropathy as well as gastrointestinal disease in a statistically significant manner.

IMMUNE-MEDIATED MUCOCUTANEOUS EXTRAINTESTINAL MANIFESTATIONS

The reactive skin lesions erythema nodosum (EN) and pyoderma gangrenosum (PG) are classically associated with IBD, with reported occurrence in 3% to 20% and 0.5% to 20% of patients, respectively [11,40,41]. EN is characterized by inflammatory nodules, typically on the extensor surface of the lower extremities but occasionally on the face or trunk. EN onset often occurs with acute flares of IBD and usually is self limiting or improves with treatment of underlying bowel disease. In contrast to EN, PG can be a more severe, and sometimes debilitating, skin condition. PG, like EN, commonly presents on the shins, initially as pustules or nodules that may evolve into painful, irregular, chronic ulcers. The correlation between bowel disease activity and the development of PG is variable [40]. Oral corticosteroids are considered the initial drug of choice for PG treatment. Alternative agents are cyclosporine and tacrolimus [15,41].

Compared with the numerous trials of infliximab in joint disease, rigorous prospective studies to investigate the effectiveness of infliximab for mucocutaneous disease in IBD are lacking. The absence of such trials is attributed to the low incidence of dermatologic EIM. Multiple positive case reports in combination with preliminary trial data, however, suggest that infliximab can heal IBD-associated skin disease, especially PG [42–47]. In the largest retrospective study to date, Reguerio and colleagues [48] described 13 cases from multiple centers of patients who had IBP with PG whose skin lesions healed completely with infliximab therapy. The study included an impressive report of a patient who had an 18-year history of multi–drug-resistant PG whose lesion healed slowly but fully after treatment with infliximab. The observed mean response time in the study was 11 days, and the observed mean complete healing time was 86 days. Brooklyn and colleagues [49] recently have published results from

the first-ever randomized, placebo-controlled therapeutic trial of infliximab for PG. T weeks after receiving one dose of infliximab, 6 of 13 infliximab-treated patients had noted improvements in their lesions, compared with only 1 of 17 placebo-treated patients. The 16 control patients who had not responded were then assigned to receive infliximab. At week 6 of the study, the investigators observed clinical responses in 20 of the 29 patients who were treated with infliximab.

Beyond PG, there are only single-case reports highlighting the therapeutic benefits of infliximab for erythema nodosum [50] and less common mucocutaneous EIM such as refractory EN, Sweet's syndrome, pyostomatitis vegetans, and metastatic cutaneous CD [51–53].

Additional evidence supporting the use of infliximab for IBD-associated mucocutaneous disease has been derived from clinical studies of psoriasis, a chronic skin condition characterized by erythematous papules and plaques with a silver scale. Like IBD, psoriasis is thought to be predisposed by immune dysregulation, and thus the two disorders share many features. In fact, psoriasis is one of the most common chronic comorbidities in patients who have IBD, and the presence of psoriasis increases a patient's risk for developing IBD [24]. Gottlieb and colleagues [54] performed a multicenter, randomized, double-blind, placebo-controlled trial investigating the effects of the infliximab loading-dose regimen (3 and 5 mg/kg) in 249 patients who had severe plaque-type psoriasis. They observed at week 10 that 158 of 198 infliximab-treated patients had at least a 75% improvement in their Psoriasis Area and Severity Indices, compared with only 3 of 50 placebo-treated patients.

IMMUNE-MEDIATED OCULAR EXTRAINTESTINAL MANIFESTATIONS

The third major area predisposed to immune-mediated EIM is the ocular system. Ophthalmologic disorders develop in 2% to 6% of patients who have IBD [11,13]; the most common are episcleritis and uveitis. Episcleritis is defined clinically as painless hyperemia of the conjunctiva and sclera with no visual deficits. Acute flares of IBD typically predispose a patient to episcleritis, with subsequent recovery with the use of anti-inflammatory agents. Uveitis, on the other hand, is an acute painful condition with associated complaints of blurry vision and photophobia. Immediate treatment of uveitis with corticosteroids is essential, because it can progress to blindness if left untreated. Similar to axial arthropathy and PG, the presentation of uveitis in IBD is not always associated with active disease. Steroid-refractory instances have been treated successfully with cyclosporine A.

As in the treatment of the mucocutaneous manifestations of IBD, less is known about the efficacy of infliximab for ocular disorders than for joint and gut disease. An increasing number of case reports and pilot studies, however, show that infliximab can suppress uveitis and scleritis associated with various autoimmune disorders including IBD [55–59]. For example, Fries and colleagues [60] reported the case of a young woman who had active CD,

acute uveitis, and sacroiliitis, all of which resolved promptly with the initiation of infliximab therapy. In another retrospective study involving seven patients who had multi–drug-resistant uveitis or scleritis and assorted systemic illnesses, six patients improved with infliximab therapy [61].

Several larger retrospective series focusing on anti-TNF therapy for pediatric uveitis have been published recently. Saurenmann and colleagues [62] reviewed treatment responses (n = 24) for 21 children who had uveitis associated with various disorders who received either infliximab (n = 13) or etanercept (n = 11) [62]. They observed that 18 of 24 treatments induced a positive response, as judged by a decreased dependency on steroids and other immunosuppressive agents. In addition, infliximab proved to significantly superior ($P = .0481$) to etanercept based on the frequency and degree of response. This difference is intriguing, given the lack of efficacy for etanercept in CD in a randomized, controlled trial [21]. In another retrospective study, 17 children who had refractory uveitis were observed to have a favorable response to infliximab (two to seven doses), with 13 of the 17 patients having no ocular inflammation after only two infusions [63].

Braun and colleagues [64] calculated the incidence of anterior uveitis flares in patients who had AS receiving anti-TNF drugs (etanercept and infliximab) or placebo in multiple placebo-controlled and open-label trials. Their analysis concluded that TNF inhibitors decreased the number of uveitis flares from 15.6 to 6.8 per 100 patient years.

Finally, Suhler and colleagues [65] performed one of the few prospective trials investigating infliximab for the treatment of refractory autoimmune uveitis. They studied the effects of the infliximab loading-dose regimen on 23 cases of uveitis. At week 10, 18 patients had responded to treatment based on a composite clinical assessment. Seven of 14 patients who went on to receive infliximab for 1 year continued to benefit from therapy.

HEPATIC INFLAMMATORY EXTRAINTESTINAL MANIFESTATIONS

Primary sclerosing cholangitis (PSC) is the most common hepatic inflammatory EIM seen in IBD. PSC is a chronic, progressive, cholestatic liver disease characterized by bile duct inflammation and fibrosis. PSC occurs in 2.4% to 7.5% of patients who have IBD, but, strikingly, 75% of patients who have PSC also have IBD, primarily ulcerative colitis [6,10]. PSC is an immuno-inflammatory EIM of IBD based on abnormalities of humoral and cellular immunity in patients who have PSC [6]. Despite this prevailing hypothesis, immunosuppressive therapy has not proven successful for PSC to date. Several case reports, however, suggest that infliximab may be able to suppress inflammatory disease activity in PSC and other hepatic EIM. Silbermintz and colleagues [66] described the complicated case of a 10-year-old young girl who was diagnosed as having CD and PSC and subsequently developed recurrent pancreatitis and granulomatous pneumonitis. Her condition worsened despite treatment with corticosteroids, methotrexate, and 6-mercaptopurine. Because the patient's various disorders were all

immuno-inflammatory EIM, infliximab therapy was initiated, after which her symptoms significantly improved. Additionally, the patient's abnormal laboratory findings, including liver-function tests, returned to normal over the short term. This case report may foreshadow future therapeutic endeavors for PSC and other IBD-related liver diseases using anti-TNF agents. Enthusiasm generated by the aforementioned cases, however, is tempered by negative reports of infliximab for PSC and by several documented cases of infliximab-mediated exacerbations of autoimmune hepatitis [67,68].

EFFICACY OF INFLIXIMAB FOR INFLAMMATORY BOWEL DISEASE AND ITS EXTRAINTESTINAL MANIFESTATIONS: A CLUE TO A COMMON MECHANISM

The clinical utility of infliximab in IBD and its EIM suggests that the pathogenesis of intestinal and extraintestinal inflammation in IBD share a common TNF-dependent mechanism. The prevailing hypothesis is that chronic mucosal inflammation in IBD is caused by a dysregulated immune response against intestinal microbial products and antigens in a genetically predisposed host [69]. The link between the joint, skin, ocular, and hepatic manifestations of IBD and immune responses against enteric microbes is not as intuitive, given the target organs' limited exposure to gut antigens. Research has provided important clues implicating a relationship between intestinal and extraintestinal inflammation. Clinicians have long recognized an association based on the observation that bowel symptoms often precede joint symptoms [11]. Interestingly, 30% to 60% of patients who have SpA without known IBD have subclinical gut inflammation, and the presence and extent of their intestinal pathology often is a direct predictor of the type and severity of their joint disease [70]. Even in the absence of microscopic colitis, the gut mucosa of patients who have SpA and CD share many immunologic similarities, including greater numbers of lymphoid follicles, a higher proportion of inflammatory T cells (T helper 1 cells), and increased expression of leukocyte adhesion molecules [71]. More detailed analyses have determined that the intestines and joints in SpA contain an abundance of TNF-expressing CD163-positive macrophages, an inflammatory cell type also found in CD tissue specimens [72]. Interestingly, infliximab therapy has been found to decrease CD163-positive macrophages in patients who have SpA. These histologic descriptions suggest that the intestinal mucosa in IBD, SpA, and possibly other EIM, is primed for antigen processing and subsequent inflammatory reactions that induce systemic inflammation, perhaps through common trafficking of inflammatory cells. TNF is an essential proinflammatory mediator of this systemic immune response, and therefore inhibition by infliximab could explain, at least in part, the multiorgan benefits of this agent in IBD.

SUMMARY

The introduction of infliximab into clinical practice is one of the most significant advances in the care of patients who have IBD. Infliximab has become

an important part of the medical armamentarium to treat extraintestinal manifestations that often are refractory to other medications and are a significant cause of morbidity in these patients. Two other TNF inhibitors recently have demonstrated efficacy in CD: certolizumab pegol [73] and adalimumab [19]. The Food and Drug Administration has approved adalimumab for use in RA. One predicts that these agents also may have activity in the extraintestinal manifestation for IBD.

To determine whether future biologics are effective in the EIM of IBD, one may need to look no further than the vast clinical trial experience in primary chronic inflammatory diseases of the joints and skin: RA and psoriasis. For example, the Food and Drug Administration recently has approved an anti–B-cell therapy, rituximab [74], and a T-cell costimulation modulator, abatacept [75], for use in RA. It certainly will be of interest to determine whether these biologic agents demonstrate efficacy in the intestinal and EIM of IBD.

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Special Article

Hepatitis B: The Pathway to Recovery Through Treatment

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Hepatitis B is a major public health problem in the world today. It is estimated that over 2 billion people have been infected with hepatitis B virus (HBV) resulting in 300 to 400 million carriers. During their lifetime, 25% of these persistently infected persons develop chronic hepatitis or hepatocellular carcinoma (HCC) resulting in 1.2 million deaths per year making hepatitis B the 10th leading cause of death worldwide. HCC is the third highest cause of death from cancer in the world, the fifth most common malignancy in males, and the eighth in females. Untreated, it yields a dismal 5-year survival between 2% and 6%.

In the United States, approximately 1.5 million people are infected with HBV. In 2003, the number of cases reported to the Centers for Disease Control and Prevention was 7526, a rate of 2.6 per 100,000 population [1]. This represents 46% of the cases of viral hepatitis reported, although it is estimated that the true incidence of hepatitis B is 15 to 30 times the reported rate. Since 1985, however, the number of reported cases has declined by over 75% (Fig. 1), presumably as a direct result of universal immunization of neonates, vaccination of at-risk populations, lifestyle or behavioral changes in high-risk groups, refinements in the screening of blood donors, and the use of virally inactivated or genetically engineered products in patients with bleeding disorders. In 2001,

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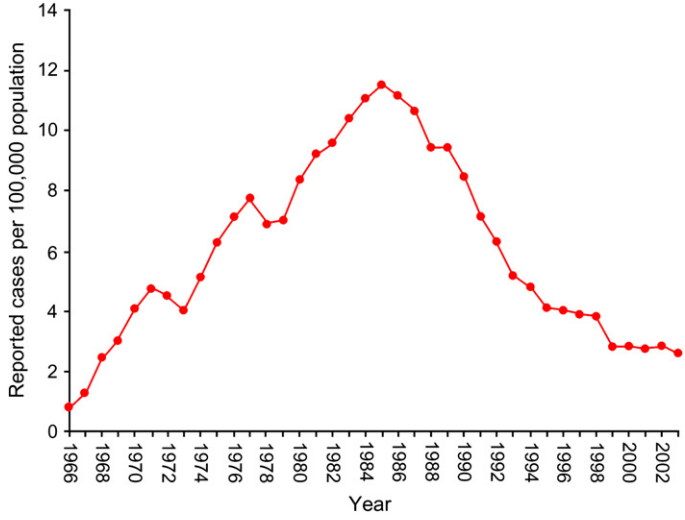

Fig. 1. Incidence of reported acute hepatitis B, United States, 1966–2003. (*Data from* Centers for Disease Control and Prevention. Hepatitis surveillance report No. 60. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.)

the authors screened over 450 Chinese-Americans in Houston, Texas, and noted an HBV carrier rate of 8.2% in that population.

INFECTIOUS AGENT

HBV is an enveloped DNA virus that initiates an infection by binding to its receptor on the hepatocytes, penetrating the cellular membrane, followed by uncoating of the virion [2]. The nucleocapsid is translocated through nuclear pores into the nucleus of the cell where the genomic DNA is matured to the covalently closed, circular DNA [cccDNA]. The cccDNA is the power source for continuing replication of the virus and is amplified during the replicative cycle. The DNA is transcribed and the resulting RNAs translated in the cytoplasm to the various viral proteins. Pregenomic RNAs are encapsidated within subviral core particles in the cytoplasm along with a viral DNA polymerase enzyme for viral DNA synthesis. Unlike most DNA viruses, it replicates by reverse transcription of the genomic RNA template. This process includes polymerization of the minus-strand DNA, degradation of the RNA intermediate, and incomplete synthesis of the plus-strand. Progeny cores bud into the endoplasmic reticulum where they acquire their envelope before undergoing vesicular transport out of the cell.

During this process, HBV production may approach 10^{11} molecules per day, although during peak replication the production rate may increase 100 to 1000 times the basal rate, which suggests that there is considerable reserve replicative capacity. Ordinarily, DNA polymerases have excellent fidelity in reading DNA

templates. Fidelity is defined as the frequency of correct nucleotide insertions per incorrect insertion. The reason for this enhanced fidelity is because when a mismatch is polymerized to the growing 3′ end of a molecule, it retards the polymerase activity leaving the mismatched nucleotide at the 3′ terminus. This delay allows spontaneous melting to occur and releases the 3′ end to contact an exonuclease site, which then excises the incorrectly added nucleotides.

In contrast to that observed with other DNA viruses, the HBV DNA polymerase lacks either fidelity or proofreading function partly because exonuclease activity is either absent or deficient in HBV. As a result, the genome, and especially the envelope gene, is mutated with unusually high frequency during replication. The mutation rate of HBV lies somewhere between the RNA-containing retroviruses, such as HIV, and other DNA viruses that lack requirements for reverse transcriptase activity. The reasons for this are not entirely clear, but may be caused by the fact that mutations in HBV are not well tolerated because over 50% of the open reading frames in the HBV genome are overlapping. For example, the HBV viral polymerase gene overlaps the pre-S/S gene and covers approximately 80% of the genome. Therefore, any mutation that occurs during replication can affect more than one open reading frame.

Electron microscopy of sera from patients with hepatitis B infection reveals the presence of three distinct morphologic entities (Fig. 2). The more numerous forms (by a factor of 10^4 to 10^6) are small, hepatitis B surface antigen (HBsAg)–positive, pleomorphic spherical particles measuring 17 to 25 nm in diameter (mean of 20 nm). Tubular or filamentous forms of various lengths, but with a diameter similar to that of the smaller particles, also are observed. Neither of these forms contains viral-specific nucleic acid, which is found in a complex, double-shelled particle with a diameter of 42 nm that comprises the hepatitis B virion. It consists of a 27-nm core surrounded by a 7- to 8-nm viral protein coat called HBsAg. This protein is identical to that detected

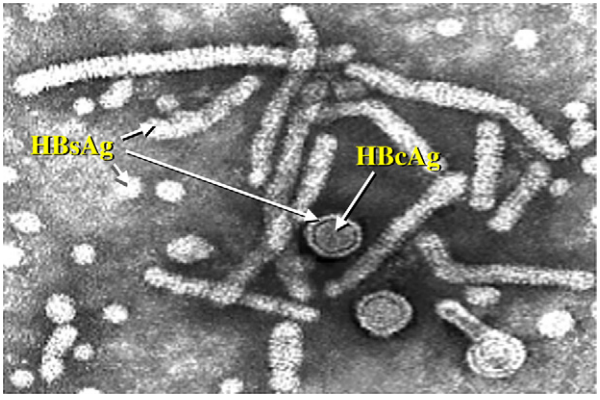

Fig. 2. Electron micrograph of hepatitis B virus. HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen.

on the smaller particles and the filaments. It contains three related glycoproteins designated S or major, M or middle (pre-S1 + S), and L or large (pre-S1 + pre-S2 + S). These proteins are not distributed uniformly between the various HBV particles that circulate in the blood. For example, the more numerous 20-nm particles (by a factor of 10,000 to 1 million) are composed primarily of the S protein, with variable amounts of the M polypeptide and essentially none of the L chains. Conversely, the HBV virion contains relatively large amounts of the L chains to M or S chains. The L chains are believed to contain the recognition site for binding to hepatocytes and are important for viral assembly and infectivity. This arrangement may be evolutionary because it prevents the significantly more numerous, noninfectious 20-nm particles, which often lack L chains, from competing for receptor sites on the surface of hepatocytes thereby interfering with infection. Increased levels of L chains also seem to down-regulate the release of the 20-nm HBsAg particles. The nucleocapsid of the virion contains a single capsid protein called hepatitis B core antigen (HBcAg). The HBV DNA is encapsidated within the nucleocapsid as a relaxed circular, partially double-stranded DNA molecule.

The viral genome has four open reading frames that code for the viral polymerase; the structural protein of the nucleocapsid (HBcAg); the viral surface glycoproteins (HBsAg); and a complex regulatory protein (X protein) that is required for infectivity. Infected individuals develop antibodies to HBsAg (anti-HBs) and HBcAg (anti-HBc) and some also generate an antibody response to the X protein. The open reading frame that codes for the core protein also codes for another protein known serologically as the hepatitis B e antigen (HBeAg). This product is not a part of the virion, and is secreted from the cell. Its accumulation in the serum is usually indicative of highly active replication of the virus. It often evokes its own antibody response (anti-HBe), which can signify a return to a less active state of viral replication. Mutant viruses with lesions in the pre-C or core promoter region of the HBV genome, however, can prevent the expression of HBeAg [3]. As a result, these patients are anti-HBe positive but may have viral replication rates that are higher than expected.

PATHOLOGY

HBV causes both acute and chronic liver disease. The pattern of liver injury is characterized by hepatocellular destruction, regeneration, and inflammatory infiltrates. Although these pathologic changes typically resolve completely after viral clearance, chronic infection is often accompanied by progressive fibrosis and architectural disarray that culminates in cirrhosis. The pattern of injury accompanying viral hepatitis has distinct features and may be distinguished from other forms of liver disease, such as cholestatic liver disease, autoimmune hepatitis, metabolic liver disease, drug-induced hepatitis, and steatohepatitis. The pattern of injury seen with acute hepatitis B, however, overlaps significantly with other causes of viral hepatitis.

Chronic Hepatitis

The histologic hallmark of chronic hepatitis B (CHB) is inflammatory destruction of hepatocytes accompanied by progressive fibrosis [4–6]. Because CHB takes decades to progress to end-stage liver disease, it is important to assess not only the pattern of injury but also the histologic severity and stage of hepatitis B. Most histologic classification systems have two scores: one based on inflammatory activities (grade) and the other on fibrosis (stage). The grade is indicative of ongoing disease activity, whereas the stage represents the cumulative effect of the disease. The inflammatory component is divided into three compartments: (1) the interface zone between the hepatocytes and the portal area (limiting plate); (2) the portal area; and (3) the hepatocellular parenchyma. Piecemeal necrosis or interface hepatitis describes the destruction of hepatocytes at the limiting plate, which forms a well-defined structure demarcating the hepatic parenchyma and the portal area. It may be focal, involving only one or two hepatocytes with little destruction of the limiting plate, or it may be extensive, involving the entire circumference of the portal area with penetration of the inflammatory cells to a depth of several hepatocytes. In more severe cases, the necroinflammatory process extends into the parenchyma, reaching to the terminal hepatic veins or to other portal areas (bridging necrosis). Lymphoid infiltrates can fill and expand the portal areas, and occasionally form aggregates of variable density.

Parenchymal inflammation in CHB generally consists of small foci of lymphocytes and macrophages surrounding apoptotic bodies or necrotic (drop-out) hepatocytes. Plasma cells and eosinophils can sometimes be seen in these foci. The relative abundance of plasma cells serves to distinguish chronic hepatitis from acute hepatitis. When these foci of lobular necrosis are the dominant features of the inflammatory pattern, it often is difficult to distinguish chronic from acute hepatitis. Regardless, this pathologic feature can be seen in many patients with CHB, particularly those with HBeAg-negative mutant infection who experience periodic flares of symptoms and biochemical abnormalities [7]. Occasionally, more extensive lobular necroinflammation with confluent, bridging, or panlobular necrosis can be seen. Frequent and severe attacks can lead to more rapid progression to cirrhosis.

Although the pattern of inflammation characterizes the pathologic process of chronic hepatitis, it is the extent of fibrosis that determines the severity and prognosis of the disease. The earliest change is an expansion of the portal area by new collagen formation. Single hepatocytes or groups of hepatocytes are surrounded by newly formed connective tissue, forming active fibrous septa. These fibrous septations gradually extend from portal areas to other portal areas or to the terminal hepatic veins (bridging fibrosis). With continued inflammation, diffuse bridging fibrosis of varying width develops and, together with regenerative changes and acinar destruction, results in the distorted architectural pattern that is recognized as cirrhosis. Cirrhosis is defined as a diffuse change of the liver in which the normal architecture is replaced by regenerative nodules surrounded by bands of fibrosis. Once

patients reach this stage, end-stage (decompensated) liver disease ensues with high morbidity and mortality.

DIAGNOSIS

Before reviewing the serologic changes that follow exposure to HBV, it is essential to have an understanding of the sensitivity of the current assays used to detect the various antigens, antibodies, and HBV DNA that circulate in the blood of infected individuals. Mass measurement units for HBsAg and HBV DNA proceed from micrograms, to nanograms, to picograms at 1000-fold intervals. Current licensed or newer enzyme immunoassays or chemiluminescent assays can detect <0.1 ng (0.1 IU or 100 pg) of HBsAg per milliliter of blood. Levels can approach 300 μg (300,000 ng) in many infected patients. However, the upper limit of detection for these assays is about 1 μg (1000 ng) per milliliter above which level saturation (a plateau) is reached. It has been estimated that you need at least 1000 20-nm HBsAg particles per milliliter of blood for current HBsAg tests to be reactive. Regardless, within the dynamic range of the test there is a direct correlation between the magnitude of the result and the concentration of antigen or antibody in the specimen, especially when paired samples are tested concurrently. If semiquantitation becomes necessary (eg, to predict resolution of the disease), the sample must be diluted until a value that falls within the dynamic range of the assay is obtained. Laboratories should report positive hepatitis serologic results in ratios in which levels ≥1 are considered reactive. A visit or call to the serology laboratory is often sufficient to obtain this information or to induce them to report the results as ratios. Confirmation of positive results is usually performed by showing that they are repeatable or, in the case of HBsAg, are specifically inhibited by unlabeled anti-HBs. Similar validation of HBsAg can be accomplished when anti-HBc (or HBV DNA, anti-HBe, or HBeAg) are detected. A common cause of nonspecific reactivity, especially with HBsAg, is usually manifested by a weakly positive response (ratios < 3) and occurs most often when testing blood that contains heparin or is from a patient with clotting abnormalities.

Nucleic acid hybridization procedures and other nucleic acid tests, such as the polymerase chain reaction (PCR) assay for the detection of HBV DNA in serum and tissue, have been important in unraveling some of the intricate immunopathogenetic mechanisms of HBV disease and for evaluating the response to antiviral therapy. Methodology for the detection of HBV DNA has gone through several innovative changes, and appreciation of their relative sensitivities is important when interpreting the published data. To place this information into perspective, it should be observed that 1 pg of HBV DNA is equivalent to about 283,000 copies or genomic-equivalents of HBV. The most sensitive assays are rapidly approaching the level of a single HBV DNA genome at least 50% of the time. For comparisons of sensitivities, it is important to convert everything to copies per milliliter or International Unit (IU) per milliliter rather than copies per reaction (or IU per reaction), because the amount of sample used to obtain a result is often different.

The dynamic range and lower limit of detection of nucleic acid assays, set at a level that detects at least 95% of the samples containing a designated amount of virus, are quite variable and, within similar products, widely divergent results can occur (Fig. 3). Results are reported in a confusing array of units including copies per milliliter, genome equivalents (gEq) per milliliter, mega-equivalents (MEq) per milliliter, and IU per milliliter. The genome equivalents per milliliter or copies per milliliter differ for each assay. To resolve this, a World Health Organization International Standard was established and arbitrarily assigned a potency of 10^6 IU/mL [8]. Assays are now being normalized to this standard, such that 1 IU/mL equals approximately 4.2 to 6.8 gEq or copies per milliliter of HBV DNA or lower.

Nucleic acid tests are prone to false-positive and false-negative results, which clinicians must appreciate when monitoring their patients. In addition, clinicians must realize that a real-time test result performed on a single sample when compared with a previous real-time test result may differ by threefold to fivefold (0.5–0.7 $\log_{10}$) even when the results are, in reality, the same. This becomes an even greater problem if the test methodology is not the same. Batch testing, in which one test is performed on multiple stored samples from the same patient, can provide results that are considered disparate if they differ by more than threefold (0.5 $\log_{10}$).

Serology

With this background, an understanding of the various clinical and serologic patterns associated with acute hepatitis B and CHB is essential for interpreting the results of the various serologic tests as summarized in Table 1 [9]. In a typical case of acute transfusion-associated HBV infection, HBV DNA is detected 2 to 5 weeks after infection and up to 40 days before the appearance of HBsAg (average 6–15 days), although newer, more sensitive HBsAg assays are closing

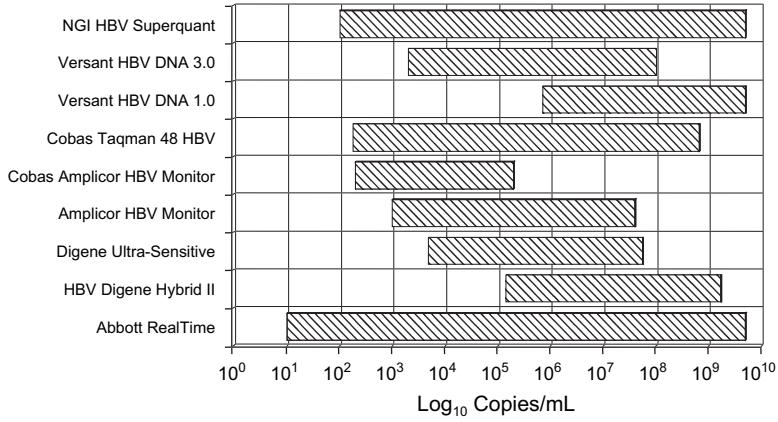

Fig. 3. Dynamic range of current and previous HBV DNA assays.

Table 1
Interpretation of hepatitis B virus serologic markers

HBV DNA	HBsAg	Anti-HBc	Anti-HBs	Interpretation
Pos	Neg	Neg	Neg	Preseroconversion window period; occult infection
Pos	***Pos***	Neg	Neg	Early acute infection
Pos	***Pos***	***Pos***	Neg	HBV infection, either acute or chronic
Neg	Neg	***Pos***	***Pos***	Previous infection with immunity (normal ALT)
Neg/***Pos***	Neg	***Pos***	Neg	Low-level carrier; early convalescent period; remote HBV infection; false-positive reaction; passive antibody
Neg	Neg	Neg	***Pos***	Vaccine-type response
Neg	Neg	Neg	Neg	Excludes HBV infection

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Data from Hollinger FB, Liang JT. Hepatitis B virus. In: Knipe DM, Howley PM, et al, editors. Fields Virology, 4th edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2971–3036.

this gap [10,11]. The HBV DNA rises slowly and circulates at relatively low levels during the early HBsAg seronegative window period (10^2–10^4 copies/mL). In contrast, viral concentrations exceeding 10^{10} HBV DNA copies per milliliter are often present during the prodromal, acute, or chronic phase of the infection. As anticipated, communicability is highest when concentrations of infectious virus attain their highest levels in the blood. This is especially true for nonparenteral (sexual) transmission. HBsAg is first detected 6 to 9 weeks after transfusion, which is 1 to 3 weeks before the alanine aminotransferase (ALT) level becomes abnormal and 3 to 5 weeks before the onset of sympase or jaundice. It reaches a peak concentration during the acute stage of the illness, and then slowly declines to undetectable levels within 4 to 6 months, although more sensitive assays can extend this time interval.

HBeAg and IgM-specific anti-HBc are usually detected subsequent to the appearance of HBsAg and concurrent with the onset of ALT abnormalities. Their appearance in the serum is indicative of ongoing viral replication. The IgM anti-HBc declines to undetectable levels regardless of whether the disease resolves or becomes chronic, but the antibody may reappear at relatively low levels as a 7S IgM fraction during reactivation of HBV as opposed to the 19S component that is present in acute disease [12,13]. IgG-specific anti-HBc generally remains detectable for a lifetime. There is no specific commercial IgG anti-HBc assay. Total anti-HBc assays measure both IgM and IgG anti-HBc.

Termination of acute HBV infection occurs with the disappearance of HBsAg and HBV DNA and the appearance of anti-HBs. Those patients who maintain high levels of HBsAg concentration throughout the infection, or those whose serum HBeAg persists 8 to 10 weeks after symptoms begin to resolve, are most likely to become chronic HBV carriers. In 21% to 32% of chronic

carriers, anti-HBs also can be detected usually in relatively low concentrations [14–16]. Many of these patients have more serious liver disease, and either the antigenic specificity of the antibody is dissimilar to the HBsAg circulating in the blood or HBV may be mutated. Using highly sensitive PCR assays, HBV DNA usually remains detectable as long as HBsAg is present in the serum.

CLINICAL FEATURES

The clinical and serologic changes that occur following infection represent a complex interaction between the virus and the host associated with an immune response to the viral infection [9]. In addition to the inapparent or subclinical cases, patients may develop anicteric or icteric hepatitis (Table 2). The terms "inapparent hepatitis" and "anicteric hepatitis" often are used interchangeably. The term "anicteric hepatitis," however, should be reserved for those patients who develop clinical symptoms but who are not jaundiced. Patients with inapparent (subclinical) hepatitis have neither symptoms nor jaundice. Symptoms ranging from mild and transient to severe and prolonged may accompany clinical hepatitis. Patients may recover completely, progress to chronic hepatitis, or develop fulminant hepatitis and die. It is important to recognize that the frequency of clinical disease increases with age, whereas the percentage of carriers decreases [17]. In endemic regions, asymptomatic perinatal acquisition of disease from HBeAg-positive mothers results in a high carrier rate of 85% to 90% [18]. In contrast, symptomatic acute infection occurs in approximately 40% of the adult-acquired infection, but the carrier rate is only approximately 2% to 5% in the absence of immunodeficiency (see Table 2) [9].

The incubation period for hepatitis B virus ranges from 45 to 120 days. Incubation periods of less than 35 days or more than 150 days are unusual. A short prodromal or preicteric phase, varying from several days to more than a week, precedes the onset of jaundice in over 85% of the HBV cases.

Table 2
Predicted outcome after an infection with hepatitis B virus

Predicted parameter	Outcome (%)
Inapparent (subclinical) or anicteric disease	65–80
Icteric disease	20–35
Complete recovery	90–98
Chronic disease (% of total number infected)	2–5[a]
Mortality rate	
Based on infection	0.2–0.5
Based on icteric cases	0.5–1.5

[a]Data compiled for adults. Infection in the perinatal period leads to chronic disease in 80%–90% of infants born to HBeAg-positive carrier mothers.

Data from Hollinger FB, Liang JT. Hepatitis B virus. In: Knipe DM, Howley PM, et al, editors. Fields Virology, 4th edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2971–3036.

Fever, if present, usually subsides after the first few days of jaundice. Occasionally, more extensive necrosis of the liver occurs. This entity, designated fulminant hepatitis B if it occurs during the first 8 weeks of illness, is characterized by the sudden onset of high fever, marked abdominal pain, vomiting, and jaundice, followed by the development of hepatic encephalopathy associated with deep coma and seizures and accompanied by severe impairment of hepatic synthetic processes, excretory functions, and detoxifying mechanisms. Although fulminant hepatitis is uncommon when compared with overall infection rates, it is observed in up to 4% of the hospitalized cases and leads to death in 70% to 90% of the patients in the absence of transplantation [19]. Recovery, when it occurs, is generally complex and without the development of chronicity.

At least one prospective study [17] indicates that higher proportions of individuals with subclinical hepatitis B are more likely to progress to chronic hepatitis (14.8% of 162) than are those who develop clinical hepatitis B (3.8% of 26). In general, chronic disease occurs in 2% to 5% of immunocompetent adults who are infected, whereas a higher rate is observed in immunocompromised patients. Previous reported higher rates of chronicity following acute hepatitis were probably inaccurate because of the fact that many of these cases were resulting from reactivation or exacerbation of unrecognized asymptomatic CHB.

Clinical Phases of Chronic Hepatitis B Virus Infection

Chronic HBV infection is defined by the persistence of HBsAg for 6 months or longer [20]. It can be classified into three major forms: (1) HBsAg carriers with inactive disease, (2) HBeAg-positive CHB, and (3) HBeAg-negative CHB. Most patients with chronic infection remain asymptomatic for many years. Some of these patients may have no clinical or biochemical evidence of liver disease. To distinguish this group from patients with chronic hepatitis, they are often categorized as asymptomatic hepatitis B carriers or simply HBsAg carriers. De Franchis and coworkers [21] recently studied the natural history of chronic HBV infection in a cohort of these patients. At baseline, 96% of 92 patients were anti-HBe positive and histologic abnormalities were normal or minimal in all but five who had only mild chronic hepatitis. During a mean follow-up of 130 months, liver enzymes remained normal in 85% of 68 patients who were extensively followed, and 13% of these patients cleared their HBsAg. Among 21 HBsAg carriers who showed no biochemical changes during 10 years of follow-up, there were no histologic changes; spontaneous reactivation was a rare event (4% of 68 patients); and no HCC was detected. Other investigators have reviewed the outcome of patients who have been histologically classified as having mild chronic hepatitis for up to 18 years [22,23]. Less than 1% of these patients progressed to cirrhosis.

CHB is the term used to describe HBeAg-positive or HBeAg-negative patients with significant chronic necroinflammatory disease of the liver associated with moderate to advanced fibrosis or cirrhosis caused by persistent HBV infection as found on liver biopsy. This is to distinguish them from the inactive (healthy) HBsAg carrier state described previously in which chronic HBV

infection is present without significant ongoing necroinflammatory disease and no or minimal fibrosis on a biopsy. Patients with moderate to severe chronic hepatitis may have no symptoms, or they may be significantly incapacitated. At the time of the initial diagnosis, jaundice is uncommon, ascites and pedal edema are seen in approximately 20%, whereas fewer than 5% present with endogenous encephalopathy or variceal bleeding. Aminotransferases, bilirubin, and gamma globulin levels are mild to markedly elevated. During follow-up, there may be a series of remissions and relapses. Remissions may last a few months to several years. During a relapse, aminotransferases may be markedly elevated and jaundice may be present. Predictors of progression to cirrhosis include hepatic decompensation; repeated episodes of severe acute exacerbation with bridging hepatic necrosis or high alpha fetoprotein levels (greater than 100 ng/mL); acute exacerbations without HBeAg clearance; and HBV reactivation with the reappearance of HBeAg [24,25].

The frequency of HBV variants differs significantly in various regions of the world as a result of the geographic distribution of the HBV genotypes. HBeAg-negative CHB is common in Asia and the Middle East, accounting for about 70% to 80% of the chronic HBV cases in those regions [26]. In contrast, an overall low prevalence of HBeAg-negative chronic HBV infection (24%) was reported in the United States in 1996 [27]. The rate of these HBV variants may have preferentially increased in the different ethnic groups, however, especially among immigrant populations from the endemic areas. In a recent cross-sectional study conducted in 17 liver centers in the United States, Chu and coworkers [28] reported that 63% of the 530 study patients had HBeAg-negative CHB. Among them, 38% had precore variants, 51% had core promoter variants, and 19% had both HBV variants.

Patients with HBeAg-negative CHB display markedly different patterns of serum aminotransferase elevations: (1) continuous elevation of ALT level in approximately 24%, (2) fluctuating ALT levels in 48%, and (3) intermittent or relapsing activities in 28% [29]. Those patients with intermittent ALT elevations could be misdiagnosed as inactive HBV carriers in between flares of hepatitis. These observations underscore the importance of regular assessments of HBsAg-positive patients over time to confirm the diagnosis of HBeAg-negative CHB versus the inactive HBV carrier. In most cases, patients require a liver biopsy. Both HBeAg-positive and HBeAg-negative CHB with persistent or intermittent elevation of aminotransferases and HBV DNA levels, associated with histologic evidence of active hepatitis, should be considered for antiviral therapy.

In one series [25], the overall annual incidence for developing cirrhosis among a group of 684 HBsAg-positive patients with CHB was 2.4% among the HBeAg-positive group and 1.3% among the anti-HBe–positive subjects, but this was not statistically significant. Unfortunately, the outcome following grading and staging of the liver biopsy at baseline was not available. For patients who already have compensated cirrhosis, the 5-year probability of survival ranges from 80% to 86% [30–32] with the cause of death being liver

failure in 53% and HCC in 35% (Fig. 4). The 5-year cumulative incidence of decompensation among compensated cirrhotics ranges from 16% to 20% [30,33] presenting as ascites in 49% or associated with jaundice in 30%. Once decompensation occurs, the prognosis is poor with 1- and 5-year survival rates ranging from 55% to 70% and 14% to 28%, respectively [30,31,34].

A proportion of hepatitis B patients, especially those who acquire the disease perinatally, are at risk of developing HCC, a tumor that is relatively slow growing with a median doubling time of 4 months (range of 1–14 months) [35,36]. Metastatic spread is uncommon, with the most frequent sites being the lung (36%); direct extension through the hepatic or portal venous systems (12%); adrenal glands (10%); skeletal tissue (10%); and brain (6%) [37]. Persons at high risk of developing HCC include adult male CHB patients with cirrhosis who contracted their disease in early childhood and who display serologic or histologic evidence of active HBV replication (HBV DNA, HBeAg, IgM anti-HBc, cytoplasmic HBcAg) [38,39]. Approximately 55% to 85% of hepatitis B patients with HCC have cirrhosis at the time of diagnosis [40,41]. Conversely, only about 5% of patients with cirrhosis develop HCC. The cumulative 5-year probability of developing HCC in HBV-infected patients with compensated cirrhosis is 9%; the incidence per 100 person-years is 2.2 [30,42]. Crockett and Keeffe [43] reviewed the relationship between various serologic patterns and the cumulative risk of HCC. The highest adjusted relative risk was found in HBsAg/HBeAg–positive patients with additional risk observed when these patients were found to be coinfected with HCV.

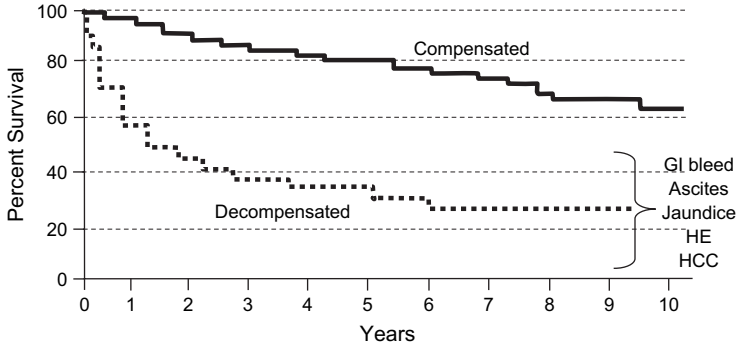

Fig. 4. Effect of decompensation on survival in patients with cirrhosis. GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy. (*Data from* Realdi G, Fattovich G, Hadziyannis S, et al. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). J Hepatol 1994;21:656–66; and Fattovich G, Giustina G, Schalm SW, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and Cirrhosis. Hepatology 1995;21:77–82.)

Recently, a great deal of interest has been generated concerning the relationship between a patient's HBV DNA level and the longer-term risk of liver cancer that is independent of HBeAg status, ALT level, and the presence of liver damage or cirrhosis [44,45]. Unfortunately, the patients in these studies usually did not have liver biopsies to document levels of fibrosis at baseline, so that the subset of patients who developed HCC within each of the HBV DNA categories could not be assessed as to risk based on histologic criteria. Chen and coworkers [44] conducted a long-term observational study on a large cohort of HBV carriers in Taiwan and found that the risk of HCC increased significantly proportional to the levels of serum HBV DNA $\geq 10^4$ copies per milliliter. It is not known, however, whether patients with low levels of HBV DNA, but relatively normal histology, are at risk, although previous studies do not support this hypothesis. It also is possible that the natural history of hepatitis B is different between endemic regions of the world where vertical and horizontal transmission is common at a young age and western countries where sexual transmission in adulthood predominates. In addition, the number of patients who acquired HCC was relatively small in this study even though the risk increased. For example, for those patients with HBV DNA levels $\leq$10,000 copies per milliliter versus those with HBV DNA levels from 10,000 to 100,000 copies per milliliter, the difference in the cumulative incidence of HCC was only 2.2% (3.5%–1.37%) over 13 years. To capture this small subset of at-risk individuals requires the treatment of over 600 people to potentially salvage <7 additional cases of HCC, assuming that treatment of HBV lowers HBV DNA levels, normalizes ALT values, or achieves HBeAg seroconversion in these patients.

Another study implied that HBV replication, as manifested by the presence of HBeAg, is hazardous in terms of disease progression and HCC development (Fig. 5) [46]. This study, however, also did not examine histology at baseline or monitor ALT levels, clinical events, or HBeAg serology during follow-up. Critical subset analyses that take into account the other known risk factors for the development of HCC (age >40 years, male gender, HBeAg positivity, excessive alcohol consumption, elevated ALT level, increased fibrosis) are necessary to establish treatment decisions, especially in adult-acquired CHB patients who have persistently normal aminotransferases and mild histology.

THERAPY FOR CHRONIC HEPATITIS B

Currently, there are five antiviral agents that are approved for the treatment of CHB by the Food and Drug Administration (FDA) in the United States. They are pegylated (PEG) and standard interferon (IFN)-α, lamivudine, adefovir dipivoxil, and entecavir. This section focuses on the application of these compounds for both HBeAg-positive and HBeAg-negative CHB.

Goals of Therapy

Goals of antiviral therapy for CHB include sustained suppression of viral replication; delayed or arrested progression of liver injury; prevention of hepatic complications, such as liver failure and HCC; and increased survival.

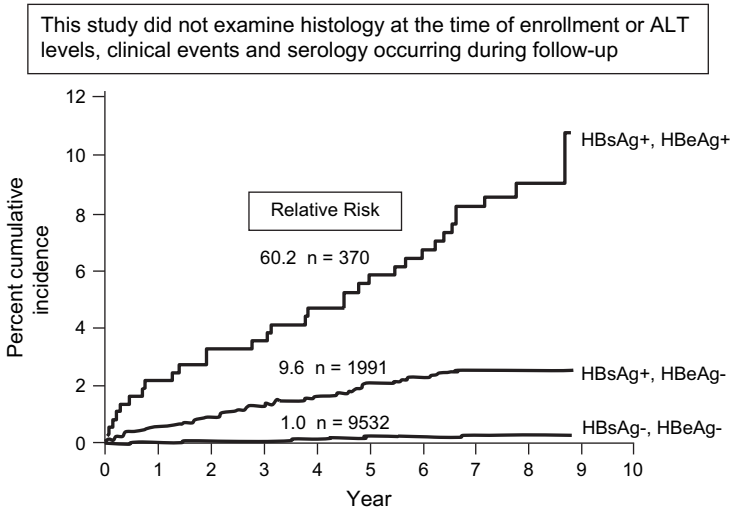

Fig. 5. HBeAg and the risk of HCC. (*Data from* Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–74.)

Complete eradication of the HBV is difficult because it has a tendency to integrate into the host genome or remain latent as covalently closed, circular DNA. Patients who become HBsAg-negative and develop anti-HBs generally have resolution of liver disease. Thus, HBsAg seroconversion should be considered a complete therapeutic response, the most desired end point of therapy.

Basic Tenets of Therapy

The most important factors associated with the development of cirrhosis and HCC are disease activity (ALT and necroinflammation on biopsy) and viral load. Hepatitis B is unlikely to progress if the patient is anti-HBe–positive, has a persistently normal ALT level, and the HBV DNA is undetectable by PCR. Serum aminotransferases and HBV DNA levels can fluctuate, however, especially in those patients with HBeAg-negative CHB; thus, isolated ALT and HBV DNA levels cannot accurately determine active or inactive disease. Liver biopsy is valuable in assessing the severity of necroinflammatory activity and fibrosis, and to guide treatment decisions in HBeAg-negative CHB and in those with viral replication but near-normal aminotransferases.

The most important short and intermediate objectives of therapy are to select potent antiviral agents that maximize and maintain HBV DNA suppression. Sustained inhibition of HBV replication is associated with normalization of aminotransferases, histologic improvement, and reduced risk of drug resistance. The long-term and ultimate goal of therapy is HBsAg seroconversion that seems to be an immune-mediated process that likely requires an immunomodulatory agent in combination with an antiviral compound.

Interferons

Standard interferon-α

IFN-α was approved as therapy of CHB in the United States in 1992. The therapeutic effects of IFN-α are secondary to its direct antiviral function; antiproliferative effect (antiangiogenic and antitumor); immunomodulatory properties; and control of apoptosis. The immunomodulatory effects of IFN-α can be recognized clinically as flares of hepatitis defined as an increase in ALT level to at least twice the baseline level. The flare often precedes a virologic response [47]. The general recommended dosage regimen for IFN-α in adults is 5 million units (MU) daily or 10 MU thrice weekly (or every other day) for 16 to 24 weeks in HBeAg-positive patients and for 12 months in HBeAg-negative patients. Furthermore, there is evidence that continuing therapy for an additional 16 weeks for the HBeAg-positive patients may be beneficial if they achieved a significant fall in HBV DNA (<10 pg/mL) but remained HBeAg positive during the first 16 weeks of treatment [48].

Hepatitis B e antigen–positive patients

Traditionally, one of the most important treatment end points for patients with HBeAg-positive CHB is the loss of HBeAg. The efficacy of IFN-α for these patients was evaluated in a well-designed meta-analysis in 1993. Wong and coworkers [49] reviewed over 25 randomized controlled studies involving a total of 837 adult patients who received interferon in doses of 5 to 10 MU given daily to 3 times weekly for 4 to 6 months. Loss of HBeAg was significantly higher among treated patients (33%) compared with controls (12%) for a difference of 21%. Importantly, loss of HBsAg occurred in 6% more of the IFN-treated patients compared with controls.

A number of long-term follow-up studies of IFN-α therapy for HBeAg-positive hepatitis have been conducted in Asia, North America, and Europe. Most of these studies compared long-term clinical outcomes in treated patients versus historical controls or treatment responders with nonresponders. Because of the differences in study designs and definition of responses, direct comparisons of the study outcomes are not possible. Several trends emerge, however, in the follow-up studies from the different geographic regions [50–52]. Studies from North America and Europe reported that 95% to 100% of treatment responders (loss of HBeAg and HBV DNA, plus biochemical remission) continued to be HBeAg-negative after 5 to 10 years of follow-up and 30% to 86% of them eventually lost HBsAg. Liver-related complications and mortality were greater in nonresponders compared with responders, especially among those with preexisting cirrhosis [50]. These studies demonstrated that the loss of HBeAg is a reliable treatment end point that is associated with long-term disease remission, and that interferon therapy is beneficial in preventing the progression to end-stage liver disease. In contrast, long-term follow-up of patients in Asian studies generally showed a lower rate of durable responses to IFN-α, and inconsistent rates of HBeAg and HBsAg clearance [53–55]. Despite the lower response, the study by Lin and coworkers [53] in Taiwan suggested that IFN therapy might

prevent the development of HCC. These differences in long-term IFN-α treatment outcomes noted in the Eastern and Western countries could reflect differences in viral factors, such as genotypes, and in the natural history of the disease in high versus low endemic areas [17].

Several factors predict the likelihood of a favorable response to IFN-α treatment in patients with chronic HBV infection, the most important of these being a high baseline ALT and low serum HBV DNA levels [56]. A flare in liver aminotransferase during treatment with IFN-α also was found to be a predictor of good response. Lau and coworkers [57] observed that 39% of patients experienced hepatitis flare on treatment. In 52% of the cases, hepatitis flare resulted in a good virologic response. The flares with favorable treatment outcomes typically occurred within the first month of therapy and were associated with a significant decrease in HBV DNA to $<10^5$ copies per milliliter at the peak of ALT elevation. Another recent study demonstrated that the degree of aminotransferase elevation during treatment has a strong predictive value for response especially for those patients with high baseline serum HBV DNA levels [58]. Although a flare in aminotransferases predicts favorable response, the IFN-α–induced flare also could precipitate decompensation in patients with cirrhosis. For this reason, IFN-α is contraindicated for patients with significant reduced hepatic reserve.

Hepatitis B e antigen–negative patients

HBeAg-negative CHB is comprised of heterogeneous disease activities and patient populations that further complicate the analysis of clinical trials and the comparisons of study results. To date, there are approximately 20 published studies using IFN for HBeAg-negative CHB. The end point of most of these studies has been loss of HBV DNA detectable by molecular hybridization (HBV DNA $<10^{5.7}$ copies per milliliter) and normalization of serum ALT within 1 year after therapy. Similar to HBeAg-positive CHB, both end-of-treatment and sustained responses are superior in treated subjects [59]. Among the controlled trials, the sustained response rate was 10% to 47% in treated subjects compared with 0% in the controls. In view of the high relapse rate ($>50\%$), an important issue is to improve the durability of response. Of note, relapses can occur months to even years after therapy [59].

In a long-term follow-up study on HBeAg-negative CHB, Manesis and Hadziyannis [60] retrospectively analyzed the clinical outcomes of 216 patients treated with 3 MU IFN alfa-2b thrice weekly for 5 or 12 months. After a median follow-up of 7 years, 18% of the patients remained in biochemical and virologic remission after a single course of therapy. Longer treatment duration (12 months) and a biochemical response within the first 4 months of therapy were identified as predictors of long-term sustained response. Encouragingly, patients with sustained response also had significant improvement of liver histology, and 32% of them ultimately lost HBsAg. This study suggests that patients with HBeAg-negative CHB require a longer course of IFN therapy to achieve complete response.

Pegylated Interferon-α

The long-acting, once weekly PEG IFN α-2a was approved by the FDA for the treatment of CHB in 2005. Cooksley and coworkers [61] performed the first randomized controlled trial of PEG IFN α-2a on 143 patients with HBeAg-positive CHB. The treatment duration was 24 weeks with 24 weeks of follow-up. Treatment response, defined by the loss of HBeAg with serum HBV DNA level below 500,000 copies per milliliter and normal ALT at the end of follow-up, was 27%, 28%, and 19% among those who received 90, 180, or 270 μg/wk of the PEG IFN, respectively. The mean response rate for the three PEG IFN groups was twice as high (24%) as the 12% observed with standard IFN α-2a ($P = .036$). The safety profiles of PEG IFN and standard IFN were similar. This encouraging result led to the development of the subsequent clinical trials that further evaluated the efficacy of both PEG IFN α-2a (40-kd branched PEG molecule) and PEG IFN α-2b (12-kd linear PEG) either alone or in combination with lamivudine (see later). The advantages and disadvantages of PEG IFN versus other FDA-approved agents are compared in Table 3. The drug is contraindicated in decompensated cirrhotics and is ineffective in patients with normal aminotransferases and high HBV DNA level.

Nucleoside and Nucleotide Analogues

Nucleoside or nucleotide analogues compete with naturally occurring purines and pyrimidines for binding to HBV DNA polymerase. They require intracellular phosphorylation for their activity. Analogues lacking a 3′-OH group on the sugar moiety result in immediate chain termination. Many of these compounds are unnatural L-enantiomers. HBV has an unusual preference for these

Table 3
Advantages and disadvantages of Food and Drug Administration–approved agents

	Nucleoside and nucleotide analogues		
Interferon	Lamivudine	Adefovir	Entecavir
Parenteral	Oral	Oral	Oral
Finite duration of therapy	Long duration	Long duration	Long duration
More durable response	Durability is limited by high rate of resistance	Suboptimal primary viral suppression in 25%	More potent than LAM
—	—	No resistance with LAM	Cross-resistance with LAM
No resistant mutants	Resistant mutants (Rx-naïve pts) 15%–30% y 1 70% y 5	Resistant mutants (Rx-naïve pts) 0% y 1, 25% y 5	Resistant mutants (Rx-naïve pts) 0% y 1 and 2
Frequent side effects	Hepatitis flares are common with resistance	Potential nephrotoxicity at high doses	Carcinogenic in rodents at very high doses only

Abbreviation: LAM, lamivudine.

products enhancing antiviral activity while diminishing cellular toxicity. The advantages and disadvantages of nucleoside and nucleotide analogues compared with IFN are listed in Table 3. Those drugs with a low resistance profile are preferable for treating patients with decompensated disease because IFN-based therapy is generally poorly tolerated.

Lamivudine

Lamivudine is a synthetic nucleoside analogue that was approved for the treatment of CHB in the United States in December 1998. Lamivudine is the (-) enantiomer of 2' -3′ dideoxy-3′-thiacytidine. The phosphorylated form (3TC-TP) exerts its therapeutic action by competing with dCTP for incorporation into the growing viral DNA chains, causing chain termination. By inhibiting both the RNA- and DNA-dependent DNA polymerase activities, the synthesis of both the first strand and the second strand of HBV DNA are interrupted [62]. Lamivudine is an oral medication and its dose for CHB is 100 mg daily. This dose was chosen based on a preliminary trial published by Dienstag and coworkers [63] who randomly assigned 32 patients to receive 25, 100, or 300 mg of lamivudine daily for a total of 12 weeks. Lamivudine therapy was well tolerated, and a daily dose of 100 mg was more effective than 25 mg and was similar to 300 mg in reducing HBV DNA levels. The loss of HBV DNA was measured by molecular hybridization (HBV DNA $<10^6$ copies per milliliter) in the study, however, so it remains uncertain whether 300 mg causes a greater decline in HBV DNA levels compared with the 100-mg regimen.

Hepatitis B e antigen–positive chronic hepatitis B

There were two large placebo-controlled trials on treatment-naive, HBeAg-positive patients performed in North America and Asia, respectively [64,65]. In both studies, 1-year therapy with lamivudine was associated with a significantly better HBeAg seroconversion (defined as loss of HBeAg, with development of antibody to HBeAg) and undetectable HBV DNA in 16% and 17% of the patients compared with a 4% and 6% response, respectively, in the placebo groups. Fall in serum HBV DNA level of ~2 $\log_{10}$ occurred in virtually all patients who received lamivudine. Among the treated patients, sustained normalization of ALT levels occurred in 41% in the North American study and 72% in the Asian study. Of note, only 70% of the Asian patients had elevated ALT levels at baseline, whereas all the patients in the North American study had abnormal ALT levels. Furthermore, both studies demonstrated an improvement in the hepatic necroinflammatory activity defined as improvement of at least two points in the Knodell score. In contrast, worsening of inflammation occurred in 30% receiving placebo. No patient in the Asian study lost HBsAg during the study, and only 2% in the North American study had undetectable HBsAg at the end of 52 weeks of treatment.

In an Asian long-term lamivudine treatment study, an incremental HBeAg seroconversion from 17% at 1 year to 27% at 2 years was observed [66]. Continuous treatment with lamivudine for 3 and 4 years was associated with HBeAg seroconversion rates of 40% and 47%, respectively [67,68].

Importantly, HBeAg seroconversion increased linearly with increasing pretherapy ALT levels. For example, Liaw and coworkers [66] showed that patients with normal ALT levels did not have HBeAg seroconversion, whereas seroconversion occurred in 23% and 80% of patients with ALT levels 2 to 5 times and >5 times the upper limit of normal, respectively. This finding was confirmed in at least two other studies showing 1-year HBeAg seroconversion rates occurring in 4%, 15%, 26% to 28%, and 56% to 64% of patients with pretreatment ALT levels within normal, one to two times normal limits, two to five times normal, and more than five times normal, respectively [69,70]. Both Asians and whites have similar rates of HBeAg seroconversion at comparable ALT levels [71]. In addition to pretreatment ALT level, histologic activity index score and body mass index have been identified as important predictors of HBeAg seroconversion during lamivudine therapy [69,70].

In another study by Liaw and coworkers [72], 436 HBV DNA–positive patients with advanced fibrosis or cirrhosis were given continuous lamivudine treatment over a median of 32.4 months (0–42 months) (Fig. 6). Clinical progression of disease was delayed by reducing the incidence of hepatic decompensation as seen by an increase in the Child-Pugh score (3.4% in the treated group versus 8.8% in those given a placebo; $P = .02$) and a decreased risk of HCC (3.9% for the lamivudine group versus 7.4% in the placebo group). YMDD mutations developed in 49% of the treated patients (versus 5% of the untreated group) and this was more likely to be associated with an increase in the Child-Pugh score. Indeed, 8 of 10 patients who died after reaching a clinical end point had evidence of YMDD mutations while receiving lamivudine.

Relapse rates after stopping lamivudine in patients who achieved HBeAg seroconversion are conflicting. Schiff and coworkers [71] observed a relapse of HBeAg in 19% of 42 patients with a response to lamivudine. In a recent study,

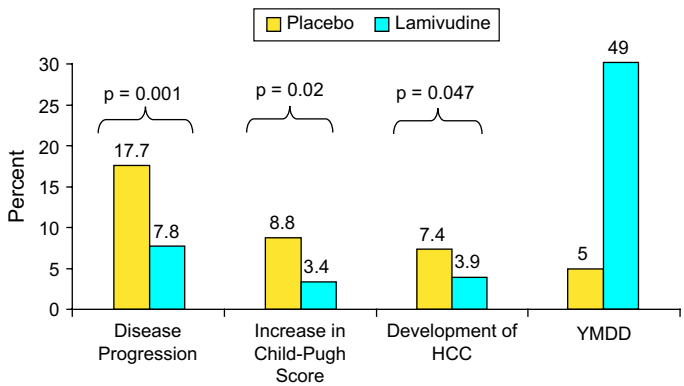

Fig. 6. Continuous treatment with lamivudine for a median of 32.4 months (0–42 months) delays the clinical progression of chronic hepatitis B. HCC, hepatocellular carcinoma. (*Data from* Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521–31.)

Dienstag and coworkers [73] followed 40 subjects with lamivudine-induced HBeAg seroconversion for a median duration of 36.6 (4.8–45.6) months. HBeAg relapse was observed at the last visit in 23% of 39 patients. Nine (22%) of 40 patients were found to be HBsAg-negative at the last assessment and 74% of 23 patients had sustained virologic and biochemical responses at the last visit. No safety issues of concern emerged. In contrast, in a retrospective Korean study in which a total of 98 patients were treated with 150 mg lamivudine daily for a mean duration of 9.3 ± 3 months, the cumulative relapse rates at 1 year and 2 years posttreatment were 38% and 49%, respectively [74]. Van Nunen and coworkers [75] combined data from 24 centers in 14 countries that yielded a total of 59 patients who responded to lamivudine therapy and showed a 3-year cumulative HBeAg relapse rate of 54% for the lamivudine-treated patients compared with 32% for IFN and 23% for those taking IFN-lamivudine combination therapy. Similarly, a Taiwanese study reported high cumulative relapse rates of 45% and 56% at 48 and 72 weeks posttreatment, respectively [76]. By multivariate analysis, pretreatment serum HBV DNA levels, pretreatment ALT levels, duration of additional lamivudine therapy after HBeAg seroconversion, and age (>25 years) have been identified as important independent predictors of posttreatment relapse [74–76].

Hepatitis B e antigen–negative chronic hepatitis B

The efficacy and safety of lamivudine were evaluated in a number of studies in HBeAg-negative patients [77–80]. In a placebo-controlled, double-blind study, response rates in 60 patients receiving lamivudine for 52 weeks were compared with 65 patients receiving placebo. Among patients in the lamivudine group, 65% had both virologic and biochemical responses (HBV DNA <700,000 gEq/mL and normal ALT) that were significantly higher than the 6% observed in the placebo group ($P < .001$). At week 52, 60% of the lamivudine-treated patients also had histologic improvement (≥2-point reduction in the Knodell necroinflammatory score) [77]. An Italian study had similar end-of-treatment biochemical and virologic responses in 87% of 15 patients at the end of 52 weeks of lamivudine therapy. All the patients relapsed within 1 to 12 months after stopping therapy, however, so sustained response was rare [78]. Hadziyannis and coworkers [79] assessed the long-term efficacy of 150 mg lamivudine daily for 24 months in 25 patients. Biochemical response was 96% at 12 months, but dropped to 60% by 24 months. Similarly, virologic response was 68% and 59% at 12 and 24 months, respectively. The decrease in rates of response over time was secondary to biochemical and virologic breakthrough [80]. Importantly, ALT increased to higher than the baseline levels in 70% of patients with a biochemical breakthrough reaching acute hepatitis levels in over 50%.

Lamivudine resistance

In general, lamivudine is well tolerated and safe even with long-term therapy in both HBeAg-positive and HBeAg-negative CHB. Unfortunately, the long-term effectiveness of lamivudine and durability of response have been compromised

by the emergence of mutations in the HBV DNA polymerase, which confers to the variant virus a selective resistance to the drug [81]. Two main mutations have been associated with such resistance: a methionine-to-valine or isoleucine substitution in the YMDD motif of the catalytic "C" domain of HBV polymerase at position 204 (M204V/I, formerly M552V/I), and a leucine-to-methionine substitution at position 180 (L180M formerly L528M) upstream of the YMDD motif in the "B" domain (Fig. 7) [82–84]. Clinically, lamivudine resistance is defined as the presence of biochemical breakthrough (increase in ALT activity greater than 1.5 times the upper limit of normal after an initial biochemical response) and virologic breakthrough (reappearance or an increase of detectable serum HBV DNA by PCR after an initial virologic response). Typically, virologic breakthrough precedes biochemical breakthrough by a median of 4 to 6 months. Studies showed that the emergence of the YMDD variant can be detected as early as 49 days after taking lamivudine, but clinically important virologic and biochemical breakthrough does not occur before 6 months [85,86]. Withdrawal of lamivudine typically leads to reappearance of the wild-type species, and subsequent repeat treatment with lamivudine is associated with a more rapid reappearance of the HBV variant [85]. In a study by Liaw and coworkers [87], acute exacerbation of hepatitis B with significant elevation of the aminotransferases (defined as five times the upper limit of normal or to a level >300 IU/L) was observed in about 30% of patients 4 to 94 weeks (median, 24 weeks) after emergence of the YMDD mutation. There was no significant difference in baseline ALT or HBV DNA levels between those who did or did not experience exacerbations. Subsequent HBV DNA levels were, however, significantly higher in patients who developed an exacerbation ($P < .005$). Acute hepatitis B exacerbation with high HBV DNA and ALT levels also has been described with the withdrawal of lamivudine therapy, and a proportion of those patients developed hepatic decompensation [88].

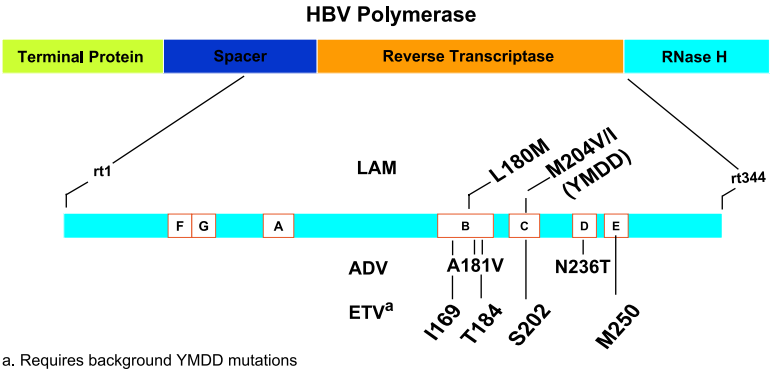

Fig. 7. Mutations in HBV polymerase related to lamivudine (LAM), adefovir (ADV), and entecavir (ETV) resistance.

In HBeAg-positive CHB, YMDD variants were reported to occur in approximately 14% of patients after 1 year of therapy [65]. With continuous treatment, the rates increased to 38% after 2 years, 53% after 3 years, and 67% after 4 years of therapy [67,68,89]. A long-term study by Leung and coworkers [67] assessed the clinical outcomes of continuous lamivudine therapy in the presence of YMDD variants in 33 patients. Fifteen of the patients who developed YMDD variants at year 2 and who continued to receive lamivudine experienced ALT flares of more than two times the upper limit of normal. Nine of the patients with lamivudine resistance had liver biopsies at baseline, 1 year, and 3 years. Worsening of the histologic activity index by 2 to 9 points was observed in six patients between the year 1 and year 3 biopsies. Approximately 25% of the patients, however, eventually achieved HBeAg seroconversion with continuous therapy despite the presence of the YMDD variants. Dienstag and coworkers [90] evaluated the histologic outcome during long-term lamivudine therapy. They found that after 3 years of continuous lamivudine treatment, 56% of 63 patients showed improvement, 33% no change, and 11% worsening. Those without YMDD variants, compared with those with, were more likely to improve (77% versus 44%) and less likely to deteriorate (5% versus 15%). Furthermore, patients with YMDD variants for more than 2 years were least likely to improve. Lau and coworkers [85] observed similar histologic responses in patients with lamivudine resistance on continuous therapy. The eight HBeAg-positive patients who developed lamivudine resistance before month 12 had no improvement in histologic activity index score. The pretreatment mean histologic activity index score was 12 compared with 11.3 at 1 year. These data suggest that continued therapy with lamivudine (up to 3 years) results in increased HBeAg seroconversion and improved histology. The studies also show, however, that continued treatment after the emergence of the YMDD variant could result in exacerbation of hepatitis, reversion of initial histologic benefits, and in some cases progression of liver disease.

In HBeAg-negative CHB, the reported rates of lamivudine resistance were variable. In a small United States study, Lau and coworkers [85] reported a low resistance rate of only 10% after 2 to 4 years of continuous therapy. In contrast, YMDD variants developed in approximately two thirds of patients within 3 years of therapy in the Mediterranean [80]. The differences could be related to the heterogeneity of the HBV. For example, most of the patients in the United States study had HBV genotypes B and C, whereas most of the study subjects in the Mediterranean had HBV genotype D. It is important to note that when the genotype D precore variant becomes YMDD-resistant, its replicative efficacy increases [91]. This observation may explain the frequent occurrence of severe virologic and biochemical breakthroughs in patients with HBeAg-negative CHB under lamivudine treatment that have been reported in studies from Greece, where there is a 95% predominance of HBV genotype D.

Papatheodoridis and coworkers [80] studied the course of virologic breakthroughs in 32 patients under long-term lamivudine monotherapy. After the onset of virologic breakthrough, the biochemical remission rate decreased from 44% at 6 months to 21% at 12 months, and 0% by 24 months. Follow-up histologic lesions in patients with biochemical breakthroughs did not differ from baseline findings. This study concludes that the emergence of viral resistance under long-term lamivudine monotherapy is usually a result of an increased HBV DNA level that culminates in the development of biochemical breakthroughs in most cases.

Predictive factors of the emergence of lamivudine resistance by multivariate analysis include high baseline HBV DNA, high baseline ALT, and high histologic activity index score [92]. Because lamivudine therapy can be associated with serious exacerbations of hepatitis, either during therapy caused by the development of drug resistance or after discontinuation of lamivudine therapy caused by relapse of wild-type HBV, patients should be closely monitored. They should have at least serum aminotransferases, and preferably also HBV DNA evaluations, every 3 months during treatment and for at least 1 year after discontinuation of therapy to allow early detection of hepatitis flares.

Adefovir Dipivoxil

Adefovir dipivoxil was approved by the FDA for treatment of CHB in September 2002. It is an oral diester prodrug of adefovir, a nucleotide adenosine analogue that, in its active form (adefovir diphosphate), inhibits HBV DNA polymerase. Because the acyclic nucleotide already contains a phosphate-mimetic group, it needs only two, instead of three, phosphorylation steps to reach the active metabolite stage. It does not depend on the virus-induced kinase to exert its antiviral action [93]. Adefovir dipivoxil has activity against wild-type, precore, and lamivudine-resistant HBV variants, and acts against a number of DNA viruses, in addition to HBV, and retroviruses (ie, HIV) [94].

Hepatitis B e antigen–positive chronic hepatitis B

In 2003, Marcellin and coworkers [95] reported results from a large phase III study involving 515 HBeAg-positive patients with CHB from 78 centers in North America, Europe, Australia, and Southeast Asia. Patients were randomized to receive either 10 or 30 mg of adefovir dipivoxil daily or a placebo for 48 weeks. Patients who received the 30 mg of adefovir had the most significant fall in serum HBV DNA levels: 4.76 log copies per milliliter compared with 3.52 log ($P < .001$) in the 10-mg dose group and 0.55 log in the placebo group. As a result, undetectable HBV DNA by PCR (less than 400 copies per milliliter) was achieved in 39% of those who received 30 mg of adefovir a day, in 21% of those who were given 10 mg a day, and in none of the placebo-treated patients. Similarly, normalization of alanine aminotransferase levels was higher in the treatment groups, 55% (30 mg) and 48% (10 mg), compared with 16% in the control group. HBeAg seroconversion occurred in 14% and 12% of the treated patients on 30 mg and 10 mg, respectively, and was infrequent (6%) in the

placebo group. Most importantly, improvement in necroinflammatory and fibrosis scores was observed in 53% and 59% of the treated patients at the end of therapy compared with 25% with placebo. The safety profile of the 10-mg dose of adefovir was similar to that of placebo. In contrast, there was a slightly higher frequency of adverse events caused by renal laboratory abnormalities in the group given 30 mg of adefovir dipivoxil per day for 48 weeks. The major potential nephrotoxicity to adefovir dipivoxil is a Fanconi-like syndrome with phosphaturia and proteinuria. The cause of the renal toxicity is related to renal tubular damage, but the exact mechanisms are not well understood. Because the 10-mg dose has a favorable risk-benefit profile for long-term treatment, it is the FDA-recommended dose for CHB. Marcellin and coworkers [96] reported long-term efficacy data with 10 mg of adefovir daily for up to week 144. The antiviral effect was maintained and there was an encouraging trend of increased HBeAg seroconversion, HBV suppression, and ALT normalization with prolonged therapy. Furthermore, there were no significant adverse events; in particular, no increased risk of nephrotoxicity was observed with prolonged therapy.

Hepatitis B e antigen–negative chronic hepatitis B

A multicenter phase III clinical trial involving 185 patients with HBeAg-negative HBV was conducted in 32 international sites [97]. The patients were randomized to receive either 10 mg of adefovir dipivoxil or placebo once daily for 48 weeks in a 2:1 ratio and a double-blind manner. The primary end point was histologic improvement at the end of therapy. Similar to the HBeAg-positive patients, the treated patients had significant histologic improvement compared with the placebo-treated group (64% versus 33%, $P < .001$). The median decrease in log-transformed HBV DNA levels was greater with adefovir than with placebo (3.91 versus 1.35 log copies per milliliter, $P < .001$) comparable with the HBeAg-positive CHB trial. Serum HBV DNA levels were reduced to fewer than 400 copies per milliliter in 51% of the patients in the adefovir group but in none of the placebo group. Alanine aminotransferase levels had normalized at week 48 in 72% of treated patients as compared with 29% of those on placebo ($P < .001$). The safety profile of adefovir dipivoxil was similar to that of placebo. At 144 weeks of therapy, the antiviral effect and histologic alterations continued to show significant improvement and no significant side effects were observed, especially nephrotoxicity. A ranked histologic assessment in HBeAg-negative CHB patients treated for 4 or 5 years with adefovir showed that $< 5\%$ of the patients had worsening of their necroinflammation or fibrosis scores [98]. Among 12 patients with bridging fibrosis or cirrhosis, seven improved at least two or more fibrosis points (on a scale of 6) during year 4 or 5 of therapy. Switching patients from adefovir to a placebo after 48 weeks resulted in a reversal of the necroinflammatory improvement seen with adefovir, whereas changing from a placebo to adefovir resulted in an opposite effect.

Because CHB is a heterogeneous disease and genotypes may influence disease progression and antiviral response, a 48-week study was performed to

analyze the antiviral efficacy of 10 mg adefovir dipivoxil with respect to HBV genotype, HBeAg serostatus, and race in patients from the two multinational phase III studies [99]. Regardless of geographic location, Asian patients were infected predominantly with genotypes B or C, whereas white patients were infected predominantly with A or D. In this study, adefovir resulted in reductions in serum HBV DNA levels independent of genotype, HBeAg status, or race. Similarly, there was no statistical difference in HBeAg seroconversion rates between genotypes.

Adefovir dipivoxil resistance

The primary site of adefovir-associated resistance mutation, N236T, is located in domain D of the HBV polymerase gene. There also is an upstream A181V substitution that is in proximity to the lamivudine L180M substitution (see Fig. 7). In vitro assays showed that HBV with the N236T substitution continues to be responsive to nucleoside analogues, such as lamivudine and entecavir [100]. In contrast, the A181V substitution had reduced responsiveness to nucleoside analogues in cell culture assays and was highly resistant to telbivudine, valtorcitabine and clevudine. It remained responsive, however, to tenofovir. These in vitro data suggest that resistance assays are necessary to identify the adefovir-induced substitutions and to guide the selection of the subsequent salvage therapy.

During the initial 48 weeks of therapy, there was no clinically important drug resistance noted in both the HBeAg-positive and HBeAg-negative CHB clinical trials [95,97,101]. In an ongoing program to monitor for the emergence of resistance in 124 patients who received continuous adefovir dipivoxil for 2 years, drug resistance developed in two (1.6%) patients [102]. With prolonged therapy, resistance was confirmed in 11%, 18%, and 28% of the study participants with HBeAg-negative CHB who continued treatment through years 3, 4, and 5, respectively [98,103]. Most of these patients exhibited viral rebound, but significant ALT flare was infrequent, and there was no worsening of liver function. Higher HBV DNA levels at year 1 are predictive of adefovir resistance development: 67% of those with HBV DNA $>$ 6 logs at year 1 developed resistance at year 3 [104]. Conversely, resistance rates were less common with lower HBV DNA: 26% among those with 3 to 6 logs, and 4% in those with $<$ 3 logs at year 1.

Entecavir

Entecavir, a cyclopentyl guanosine nucleoside analogue, is a selective inhibitor of HBV replication. It has no antiviral activity against HIV. Entecavir blocks all three polymerase steps involved in the replication process of the hepatitis B virus: (1) base priming, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV DNA. It is more efficiently phosphorylated to its active triphosphate compound by cellular kinases compared with other nucleoside analogues. It is a potent inhibitor of wide-type HBV but is less effective against lamivudine-resistant HBV mutants [105].

In a 24-week, double-blind, randomized, phase II dose-finding clinical trial, 169 patients with CHB were evaluated [106]. The safety and efficacy of entecavir (0.01 mg/d, 0.1 mg/d, or 0.5 mg/d orally) were compared with lamivudine (100 mg/d orally). A dose-response relationship was observed with entecavir in HBV DNA suppression. At 22 weeks of therapy, 84% of patients treated with entecavir had an HBV DNA level below 0.7 MEq/mL by the branched DNA assay, compared with 58% treated with lamivudine ($P = .008$). Entecavir was well tolerated at all doses and the side effect profile was similar to lamivudine. Entecavir at 0.5 mg daily was subsequently chosen as an effective and safe dose for the treatment of naive patients and was further evaluated in phase III clinical trials.

Hepatitis B e antigen–positive chronic hepatitis B

A multinational phase III randomized, double-blind study was conducted in nucleoside therapy–naive patients with HBeAg-positive CHB [107]. Seven hundred and nine patients were randomized to entecavir, 0.5 mg once daily, or lamivudine, 100 mg once daily, for 48 weeks. The primary end point of the study was histologic improvement at week 48 of therapy. It was defined as ≥2-point decrease in the Knodell necroinflammatory score and no worsening of fibrosis from baseline. A significantly higher proportion of the patients in the entecavir treatment arm (72%) achieved this treatment end point when compared with the lamivudine arm (62%; $P = .0085$). Furthermore, 67% of the entecavir-treated patients had undetectable HBV DNA (<300 copies per milliliter by PCR assay) at week 48 compared with 36% of those on lamivudine ($P < .0001$) (Fig. 8). Of note, the baseline HBV DNA levels were comparable in both groups: 9.62 and 9.69 log copies per milliliter in the entecavir and lamivudine arms, respectively. Entecavir also was superior to lamivudine for the

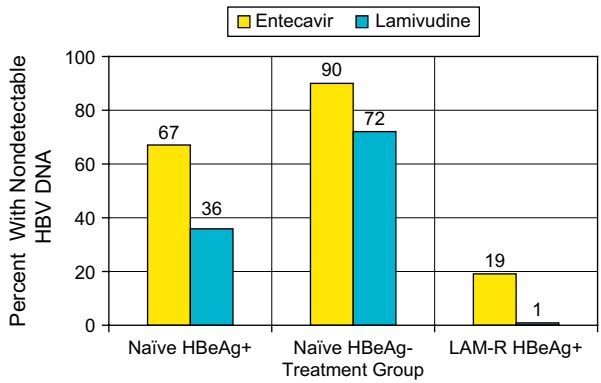

Fig. 8. Percent of chronic hepatitis B patients with nondetectable HBV DNA (<300 copies/mL) at week 48 of therapy with entecavir by HBeAg and lamivudine refractory status ($P \leq .001$). HBeAg, hepatitis B e antigen; LAM, lamivudine. *Data from* references 108, 110, and 112.

proportion of patients with ALT normalization ($\leq 1 \times$ upper limit of normal) at week 48 (68% versus 60%, respectively; $P = .02$). HBeAg seroconversion, however, was similar for both the entecavir (21%) and lamivudine (18%) treatment groups at week 48. With prolonged therapy at year 2, entecavir treatment was associated with an increased rate of HBeAg seroconversion to 31% compared to 26% with lamivudine. A higher proportion of the patients in the entecavir arm also achieved undetectable HBV DNA at year 2 compared with lamivudine, 31% versus 26% [108].

Hepatitis B e antigen–negative chronic hepatitis B

A multinational, randomized, double-blind study, investigated the safety and efficacy of entecavir versus lamivudine in 638 nucleoside-naive patients with chronic HBV infection who were HBeAg-negative [109]. The study design was similar to the HBeAg-positive trial. Patients were randomized to receive 0.5 mg entecavir once daily versus 100 mg lamivudine for 48 weeks. Histologic improvement at week 48 was observed in 70% of the entecavir-treated patients versus 61% of the lamivudine group ($P = .014$). The baseline HBV DNA levels were comparable in both groups: 7.6 and 7.55 log copies per milliliter, respectively. At week 48, entecavir treatment was associated with a significantly higher rate of HBV DNA suppression to <300 copies per milliliter compared with lamivudine (90% versus 72% with $P < .0001$) (see Fig. 8). ALT normalization was 78% in the entecavir arm compared with 71% in the lamivudine arm ($P = .045$).

Entecavir resistance

The development of entecavir resistance requires pre-existing lamivudine resistance mutations and additional changes in the HBV polymerase: T184, I169 in domain B, S202 in domain C, or M250 in domain E (see Fig. 7) [110]. Among all the nucleoside treatment–naive patients in both the HBeAg-positive and HBeAg-negative CHB clinical trials who completed 2 years of entecavir therapy, there was no evidence of emerging entecavir substitutions. Among HBeAg-positive, lamivudine-refractory CHB patients who were switched to entecavir for 48 weeks (see Fig. 8), 19% had nondetectable HBV DNA (<300 copies per milliliter by PCR) versus only 1% in those continued on lamivudine [111]. For patients with lamivudine resistance who were subsequently switched to entecavir, virologic rebound (confirmed as >1 $\log_{10}$ increase from nadir by PCR) caused by resistance was observed in 1% of the patients in year 1 [112]. In all cases, entecavir mutants had pre-existing lamivudine resistance substitutions and emerging changes at T184 or S202. In contrast, although there was no evidence of entecavir resistance in nucleoside treatment–naive subjects, after 2 years of continuous therapy 10% of lamivudine-refractory patients experienced resistance to entecavir. Thus, phenotypic entecavir resistance seems to require the presence of pre-existing lamivudine resistance substitutions.

Combination Therapy

After evaluating the efficacy and limitations of each agent for the therapy of CHB, it is logical to examine a combination of the drugs with different

mechanisms of actions to optimize the suppression of HBV and to improve both the short- and long-term responses. Mathematical modeling of the HBV kinetics with nucleotide analogue therapy (adefovir) showed a biphasic decline of the HBV levels. The initial, faster phase of viral load decline reflects the clearance of HBV particles from plasma. The second, slower phase of viral load decline closely mirrors the rate-limiting process of infected cell loss [113]. Because the second phase of viral decline is likely to be induced by an immune-mediated process, the immune clearance of the virus should be up-regulated by immunomodulators, such as the IFNs. This suggests that there may be at least a theoretical advantage to the use of nucleoside and nucleotide analogues with IFN in combination.

Nucleoside analogues and pegylated interferon

There are a number of published multicenter clinical trials using a combination of lamivudine and PEG IFN-α. Two large randomized, controlled trials focused on HBeAg-positive patients and one on HBeAg-negative CHB [114–116]. In the study conducted by Janssen and coworkers [114], 307 HBeAg-positive patients were randomized to receive either a combination of PEG IFN α-2b, 100 μg/wk for 32 weeks then 50 μg/wk for 20 weeks, in combination with lamivudine, 100 mg/d, or PEG IFN α-2b with placebo. At 26 weeks follow-up, no difference in efficacy end points was found between the PEG IFN monotherapy and combination therapy, which used a relatively low dose of PEG IFN. Both groups achieved similar rates of HBV DNA suppression to <400 copies per milliliter (7% versus 9%); HBeAg loss (36% versus 35%); and ALT normalization (32% and 35%). Both regimens resulted in a relatively high rate of HBsAg loss at 7% in 1 year. Besides elevated baseline ALT levels, HBV genotype also was identified to be a predictor of response: 60% of the genotype A patients responded compared with 42% for genotype B, 32% for genotype C, and 28% for genotype D.

Lau and coworkers [115] reported results on another large randomized controlled trial comparing the efficacy and safety of PEG IFN α-2a (180 μg weekly), PEG IFN α-2a (180 μg weekly) with lamivudine (100 mg daily), and lamivudine (100 mg daily) alone for 48 weeks in 814 HBeAg-positive patients. At 24 weeks of follow-up, the two PEG IFN treatment arms (with or without lamivudine) showed the same efficacy, and were superior to that observed in the lamivudine arm alone (Fig. 9). Applying a similar study design, Marcellin and coworkers [116] evaluated the efficacy and the safety of PEG IFN α-2a alone or in combination with lamivudine versus lamivudine for 48 weeks in 537 patients with HBeAg-negative CHB. At the end of the 24-week posttreatment follow-up, the two PEG IFN treatment arms (with or without lamivudine) again showed similar efficacy and were superior to the lamivudine treatment (Fig. 10). Importantly, there was a higher rate of lamivudine resistance in the lamivudine monotherapy arm (18%) compared with the PEG IFN α-2a plus lamivudine combination arm (<1%) at week 48 ($P < .001$). These studies concluded that the combination of PEG IFN α-2a with

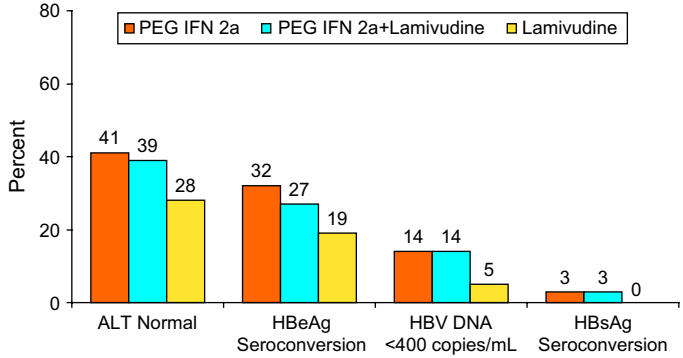

Fig. 9. Biochemical and virologic end points after 48 weeks of therapy and 24 weeks of follow-up in 814 HBeAg-positive chronic hepatitis B patients. HBeAg, hepatitis B e antigen, IFN, interferon; PEG, pegylated. (*Data from* Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352:2682–95.)

lamivudine is not superior to PEG IFN α-2a alone. The PEG IFN combination, however, reduced the risk of lamivudine resistance.

Combined nucleoside and nucleotide analogues

To date, there have been limited data on the efficacy of combining nucleoside and nucleotide analogues. Lau and coworkers [117] evaluated combination therapy with lamivudine and famciclovir in 21 HBeAg-positive Chinese patients. They found that patients who received lamivudine, 150 mg daily, and famciclovir, 500 mg three times daily, had a more rapid fall in HBV DNA

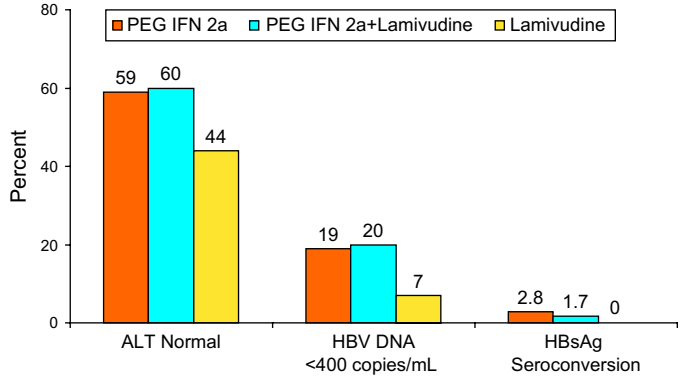

Fig. 10. Biochemical and virologic responses after 48 weeks of therapy and 24 weeks of follow-up in 537 HBeAg-negative chronic hepatitis B patients. HBsAg, hepatitis B surface antigen, IFN, interferon; PEG, pegylated. (*Data from* Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351:1206–17.)

levels and a higher rate of HBeAg loss compared with those on lamivudine monotherapy. A recent study compared the efficacy of adefovir with lamivudine versus lamivudine alone in 112 treatment-naive, predominantly HBeAg-positive patients [118]. The rates of undetectable HBV DNA by PCR (39% and 41%) and HBeAg loss (19% and 20%) were similar in the two arms. It is important to mention, however, that there was a significantly lower rate of lamivudine resistance in the combination group (2%) compared with lamivudine monotherapy (20%) ($P \leq .003$).

Although the combination regimens evaluated so far did not seem to improve efficacy, they did reduce the rates of resistance to nucleoside or nucleotide monotherapy (see previously). A number of promising nucleoside analogues, such as tenofovir, emtricitabine, clevudine, and valtorcitabine are being vigorously evaluated in national and international multicenter clinical trials to identify effective combination therapies. An optimal combination regimen should work synergistically in viral suppression, increase rates of HBeAg and HBsAg seroconversion, and prevent the occurrence of viral resistance. In view of an increased rate of viral mutation in immunocompromised hosts, a combination of tenofovir plus lamivudine or emtricitabine should be considered for HBV/HIV coinfected patients who require an antiretroviral regimen [94].

Current Treatment Recommendations

The goals of therapy for CHB are to achieve sustained viral suppression and improve clinical outcome, decreasing the risk of cirrhosis, HCC, and ultimately the complete resolution of liver disease. There are a number of published treatment guidelines for CHB [119,120]. It must be kept in mind, however, that treatment needs to be tailored to the individual patient because HBV is a heterogeneous disease with variable manifestations. The severity of liver disease, efficacy, potential complications, and cost of the therapeutic agents need to be considered carefully before initiating a course of therapy.

Table 4 presents the authors' perspective on the treatment of chronic hepatitis B based on the principles discussed in this article. It is important to point out that treatment decisions need to be governed by serial HBV DNA and ALT determinations rather than isolated laboratory values. The HBV DNA levels chosen are somewhat arbitrary and one must examine all the host and viral factors in decision making. Liver biopsy can be a valuable tool in the setting of fluctuating hepatitis, viral levels, or persistently normal or near-normal aminotransferases.

In the authors' opinion, lamivudine should no longer be used routinely as the first line of therapy because of its high rate of resistance. Lamivudine continues to have a role in the setting of shorter-term prophylaxis, such as the prevention of HBV reactivation during chemotherapy, or the vertical transmission of HBV in pregnant women with high levels of viremia in conjunction with hepatitis B immune globulin and vaccine of their infants at birth to ensure optimal protection. Careful selection of a first-line agent is necessary to avoid not only resistance,

Table 4
A perspective on the treatment of chronic hepatitis B

HBeAg	HBV DNA	ALT	Treatment strategy
+	+[a]	≤2 × ULN	Lower efficacy with current treatment Observe and consider treatment when ALT becomes elevated
+	+	>2 × ULN	Peg-IFN-α, ADV or ETV; ADV or ETV for Peg-IFN-α NR/contraindications
−	+[b]	>2 × ULN	Peg-IFN-α, ADV or ETV (oral agents may be preterred because of need for long-term treatment); ADV or ETV for Peg-IFN-α NR/contraindications
−	−	≤2 × ULN	No treatment needed; observe for hepatitis reactivation
+/−	Detectable	Cirrhosis	Compensated: ADV or ETV Decompensated:ADV or ETV; refer for liver transplant and coordinate treatment with transplant center
+/−	−	Cirrhosis	Compensated: observe and treat with oral agents if HBV DNA becomes positive Decompensated:refer for liver transplant

Abbreviations: ADV, adefovir; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IFN, interferon; NR, nonresponders; PEG, pegylated; ULN, upper limit of normal.
[a]HBV DNA $>10^4$ or $>10^5$ copies/mL (arbitrary decision without unanimity).
[b]HBV DNA $>10^4$ copies/mL (arbitrarily chosen).

but also the development of cross-resistance to other agents. When resistance to first-line therapy does develop, alternative therapy should be considered. In addition, surveillance of HCC in regular intervals should be considered even for those whose treatment is deferred, especially if they have risk factors [121].

Future hepatitis B consensus conferences will supplement these recommendations. Regardless, most experts would agree that the ideal end points to any therapy are to achieve permanently undetectable HBV DNA levels by PCR; a normal ALT level; HBeAg seroconversion (in HBeAg-positive patients); HBsAg seroconversion; and clearance of covalently closed, circular DNA from hepatocytes. With the increased number of new and potent antiviral agents being developed and evaluated, it provides hope and optimism for those who are chronically infected with HBV. One must not lose sight of the fact, however, that prevention remains the most effective strategy in the global management of HBV. Universal immunization programs will not only prevent HBV transmission and circumvent acute and chronic infection, but they will also interdict hepatitis delta infection and HCC.

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