Biologic therapies for inflammatory bowel disease (IBD) have revolutionized the treatment of patients with Crohn's disease and have begun to have an impact on therapy for refractory ulcerative colitis. Biologic therapies have been highly effective, especially for patients with corticosteroid-dependent, corticosteroid-refractory, or fistulizing disease. Accumulating evidence in other immune-mediated diseases, such as rheumatoid arthritis, and emerging evidence from IBD research suggest that these agents not only control symptoms but also may potentially alter the natural course of disease. Balancing the proven and potential efficacies, however, are the economic costs and the risks of serious, potentially severe side effects associated with biologic therapy. Thus, the appropriate role for these agents in the clinical care of patients with IBD continues to evolve.

To provide clinicians with information about the benefits and risks associated with these medications and with guidance regarding their appropriate use, the American Gastroenterological Association Institute convened an IBD Biologics Consensus Conference on June 21–23, 2006. During the first day of the conference, international experts in gastroenterology and immunology (Appendix 1) presented the most recent pharmacologic, clinical, and epidemiologic research concerning biologics and their use (conference agenda, Appendix 2). These presentations addressed key questions regarding indications for, appropriate administration of, and comparative efficacy, toxicity, and immunogenicity of biologics. Subsequently, the IBD Biologics Consensus Conference Panel, composed of IBD experts from Europe and North America (Appendix 1), developed a consensus statement pertaining to the role of biologics in IBD therapy and identified important unanswered questions for future research. The executive summary of this report contains the panel’s recommendations for use of biologics in IBD and the panel's opinion regarding the strength of the data on which these recommendations are made. The body of this report summarizes the panel’s conclusions regarding the current applications, potential complications, and controversies related to biologic therapies in IBD. Readers are encouraged to read the report in its entirety.
questions regarding the appropriate role of biologics in IBD care. The IBD Biologics Consensus Panel has attempted to address these issues.

Process

The panel evaluated available evidence based on the Oxford criteria, a system that grades individual studies based on study design and strength of results (Table 1) and subsequently designates the strength of the aggregated evidence1 (Table 2). Indications assigned an “A” have consistent high-quality (level 1) studies supporting their use. Those designated “B” are recommended based on consistent level 2 or 3 studies or extrapolations from level 1 studies, “C” level recommendations indicate that only level 4 studies or extrapolations from level 2 or 3 studies exist, and “D” indicates generally poor, level 5 evidence or troublingly inconsistent or inconclusive studies of any level. Where no clinical data exist, the panel has noted this. Since the panel’s meeting, the Food and Drug Administration has notified UCB that it will need to conduct another trial of certolizumab pegol for CD, thus delaying its potential approval for a number of years.

Consensus Panel Recommendations: Overview

While novel biologic agents continue to be developed, the majority of data to date relate to anti–tumor necrosis factor (TNF) therapy in general and infliximab in particular. There is expanding and robust evidence for alternative anti-TNF strategies and monoclonal antibodies targeting adhesion molecules, as well as other less “mature” biologic agents and targets. Already, anti-TNF agents have been shown to induce and maintain remission effectively in moderate to severe CD and UC. However, despite emerging evidence that early use of biologics has the potential to modify disease course, data to date do not support their routine use as first-line agents. The use of biologics can be considered before use of corticosteroids in patients for whom other therapies have failed, when corticosteroids are contraindicated, or in specific patient subgroups, such as those with complex fistulas, where conventional therapies are relatively ineffective.

Relative efficacy, safety, and contraindications within anti-TNF class. When comparing anti-TNFs with each other, the panel concluded that despite the limitations inherent in comparing clinical trials of differing designs, currently available anti-TNF agents approved for treatment of CD (infliximab and adalimumab) and UC (infliximab) and those whose approval is anticipated within the next year (certolizumab pegol), when optimally dosed, are similarly effective in their ability to induce response and remission. Head-to-head comparisons in trials are necessary to compare efficacies. The rapidity of response may vary by agent, and the mode of administration may affect differing immunogenicity and convenience profiles. The degree of these differences and their overall clinical relevance remain unknown. In contrast, in doses that are effective in rheumatoid arthritis, the soluble TNF receptor etanercept is not effective in CD.

The development of antibodies against biologic therapies is common and can decrease the degree and duration of therapeutic response. The mechanisms, consequences, and prevention of immunogenicity require further study; however, current data suggest that high-dose induction accompanied by scheduled maintenance regimens can

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**Table 1. Study Design and Strength of Results**

<table>
<thead>
<tr>
<th>Individual study</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Systematic review (SR) with homogeneity of Level 1 diagnostic studies</td>
<td>Systematic review (SR) with homogeneity of randomized controlled trials (RCTs)</td>
</tr>
<tr>
<td>1b Validating cohort study with good reference standards</td>
<td>Individual RCT (with narrow Confidence Interval)</td>
</tr>
<tr>
<td>1c Specificity is so high that a positive result rules in the diagnosis (“SpPin”) or sensitivity is so high that a negative result rules out the diagnosis (“SnNout”)</td>
<td>All or none</td>
</tr>
<tr>
<td>2a SR with homogeneity of Level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity) of cohort studies</td>
</tr>
<tr>
<td>2b Exploratory cohort study with good reference standards</td>
<td>Individual cohort study (including low quality RCT; eg, &lt;80% follow-up)</td>
</tr>
<tr>
<td>2c SR with homogeneity of 3b and better studies</td>
<td>“Outcomes” Research; Ecological studies</td>
</tr>
<tr>
<td>3a Non-consecutive study; or without consistently applied reference standards</td>
<td>SR with homogeneity of case-control studies</td>
</tr>
<tr>
<td>3b Case-control study, poor or non-independent reference standard</td>
<td>Individual Case-Control Study</td>
</tr>
<tr>
<td>4 Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
<td>Case-series (and poor quality cohort and case-control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
</tr>
</tbody>
</table>

**Table 2. Strength of the Aggregated Evidence**

- A consistent level 1 studies
- B consistent level 2 or 3 studies or extrapolations from level 1 studies
- C level 4 studies or extrapolations from level 2 or 3 studies
- D level 5 evidence or troublingly inconsistent or inconclusive studies of any level
reduce the immune response. In addition, concomitant immune suppression reduces the development of antibodies for all biologic agents described in this report. The development of immunogenicity results in lower serum levels of the biologic agents, which can reduce the efficacy of an individual agent and increase the likelihood of infusion reactions during and after intravenous administration. It should be noted that azathioprine and 6-mercaptopurine require many weeks to reach peak effects. The lead time for immunomodulatory effects of methotrexate is also not established. Thus, adequate immune suppression dictates that these medications be initiated in advance of biologic therapy. Whether continuous biologic therapy alone is sufficient to prevent antibiologic response or whether concomitant use of immune suppression is necessary to optimize the long-term effectiveness of biologics remains unclear. The use of these approaches will depend on their long-term safety profiles and on whether alternative agents are available for substitution if there is a loss of response to the initial biologic therapy.

All anti-TNFs have similar safety profiles. Anti-TNFs increase the risks of infections, particularly due to intracellular pathogens such as tuberculosis. Infusion and injection site reactions occur with all anti-TNFs, although rates vary by mode of administration. Patients frequently develop serologic evidence of autoimmunity (elevated concentrations of antinuclear antibody) after exposure to infliximab. The frequency of autoantibodies is less with adalimumab, certolizumab pegol, and natalizumab. The relevance of autoantibodies is unclear because drug-induced lupus is rare.

Relative efficacy, safety, and contraindications: anti-TNFs and natalizumab. Natalizumab has not been directly compared with any anti-TNFs in the treatment of IBD. Review of similarly designed clinical trials, however, indicates that natalizumab has similar maintenance benefits to anti-TNFs, although there are less high-quality data to evaluate pertaining to induction of remission (eg, patients without elevated C-reactive protein [CRP] levels). In general, when administered without concomitant immune suppression, anti-TNF therapies and natalizumab have similar rates of complications such as infection and neoplasia. The specific types of infection and neoplasia, however, may vary between agents.

The risks of immunogenicity with natalizumab administration appear similar to those attendant to anti-TNF use and also appear to be modified by concomitant immune suppression. The use of immune suppression with anti-TNF agents and natalizumab, however, appears to increase the risk of serious infections, such as progressive multifocal leukoencephalopathy (PML), a rare and devastating neurologic illness associated with natalizumab use, and neoplasia, such as hepatosplenic T-cell lymphomas associated with combined use of infliximab and azathioprine. These uncommon but serious risks require additional risk-benefit evaluations for individual patients.

Future Directions in Biologic Therapy

The numbers and roles of biologics in IBD are likely to continue expanding. Emerging data suggest that biologics may have the potential to prevent complications and limit disease progression. If such benefits are proven, biologics may be used in the future to modulate subclinical inflammation and to prevent development of clinical disease. Ongoing research may identify roles for biologic therapies in a broad range of clinical scenarios, including limited (bridge) therapy, combination therapy, sequential therapy to maintain remission induced through surgery or through the use of nonbiologic therapies, in pregnant patients, and in the treatment of extraintestinal manifestations of IBD. The continued development of biologic therapies is poised to continue the rapid transformation of IBD treatment.

Consensus Panel Recommendations: Specific Recommendations

Infliximab (Remicade). Indications for infliximab in CD.

- Induction of response
  - In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (A, adults; B, children)

- Induction of remission
  - In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (A, adults; B, children)
  - Induction of mucosal healing (C)

- Maintenance of response to infliximab (A, adults; A/B, children)
- Maintenance of remission after infliximab (A, adults; A/B, children)
- Hospitalized severe patients (D)
- Induction of response in outpatient adults with draining perianal fistulas who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (A)
- Induction of response in outpatient adults with draining abdominal or rectovaginal fistulas who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (C)
- Steroid sparing (C)
● Extraintestinal manifestations of CD
  – Spondyloarthropathy (A)
  – Arthritis/arthritis (C)
    – Pyoderma gangrenosum (B) and erythema nodosum (D)
  – Uveitis and other ocular manifestations of CD (C)
    Except optic neuritis, which may be precipitated or aggravated by anti-TNF medications

**Indications for infliximab in UC.**

● Induction of response
  – In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, corticosteroids, or immunomodulators (A, adults; C, children)

● Induction of remission
  – In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, corticosteroids, or immunomodulators (A, adults; C, children)
  – Mucosal healing (B)

● Maintenance of response to infliximab (A, adults; C, children)

● Maintenance of remission after infliximab (A, adults; C, children)

● Hospitalized severe patients (B)
  – Role in acute severe (“fulminant”) UC is not yet proven

● Steroid sparing (B)

● Extraintestinal manifestations of UC
  – Spondyloarthropathy (A)
  – Pyoderma gangrenosum (B)

**Infliximab dosing: all indications.** Initial dosing for infliximab is generally agreed upon. There is less agreement, however, regarding the total number and frequency of dosing and the role for increased dosing. Specifically, among patients who have not responded to 2 initial doses of infliximab, the value of a third dose is not established. Similarly, although single infliximab infusions have proven efficacious, they are associated with higher rates of antibody formation that may seriously limit its future use. Similarly, there are insufficient data to compare immunogenicity of induction with a 0-, 2-, and 6-week schedule followed by regularly scheduled infusions every 8 weeks compared with regularly scheduled infusions every 8 weeks.

● Recommended dosing for all indications is 5 mg/kg body wt given as an intravenous infusion over 2 hours in an induction regimen of 3 doses at weeks 0, 2, and 6, followed by maintenance dosing every 8 weeks beginning at week 14 in patients who have responded to the induction regimen.
  – Evidence of benefit of 6-week infusion has not been established.

● Induction therapy without maintenance has been efficacious in corticosteroid-naive patients when used with concomitant immune suppression.

● A single dose has been shown to be effective but has been associated with higher rates of immunogenicity, antibody to infliximab formation, which has been associated with infusion reactions and subsequent attenuation or loss of response.

● Primary nonresponse can be determined after 2 doses.
  – The additional benefit from a third infusion in patients not responding to the first 2 infusions has not been shown. Patients not responding to the initial 2 doses should be discontinued from this therapy.

● Patients who have attenuated response may be given
  – higher dose infusions up to 10 mg/kg at 8-week intervals, or
  – 5 mg/kg at shortened intervals as frequently as every 4 weeks.

**Adalimumab (Humira). Indications for adalimumab in CD.**

● Induction of response
  – In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (A, adults; C, children)

● Induction of remission
  – In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (A, adults; C, children)
  – Mucosal healing has not been studied

● Maintenance of response after adalimumab (A, adults; C, children)

● Maintenance of remission after adalimumab (A, adults; C, children)

● Loss of response or intolerance to infliximab (A)
  – Somewhat lower absolute response rates than in anti-TNF naïve patients

● Induction of response in outpatient adults with draining perianal fistulas who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (A, adults; C, children)
licylates, antibiotics, corticosteroids, or immunomodulators (C)

- Steroid sparing (B)

- Extraintestinal manifestations of CD
  - Spondyloarthropathy (A)
  - Arthritis/arthralgia (D)
  - Pyoderma gangrenosum (A)
  - Uveitis (D)

**Adalimumab in UC.** Insufficient data currently support the use of adalimumab in the treatment of UC.

**Adalimumab dosing in CD.**

- Recommended dosing is 160 mg subcutaneously (SC) on day 1 of week 0, followed by 80 mg SC on day 1 of week 2.
  - 80 mg followed by 40 mg may also be effective (demonstrated in open-label induction phase of the CRohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance [CHARM] study).
  - Subsequent response in 4-week nonresponders has not been established.

- Patients who respond to the induction regimen should continue on a maintenance regimen of 40 mg SC every other week.

- Patients who have suboptimal response to 40 mg SC every other week may increase frequency of dosing to 40 mg SC weekly
  - Or 80 mg every other week.

- Episodic dosing has not been evaluated and may increase immunogenicity.

**Certolizumab pegol (Cimzia).** *Indications for certolizumab pegol in CD.*

- Induction of response
  - In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (A, adults; children, not yet studied)

- Induction of remission
  - In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators (C, adults; children, not yet studied)
  - Mucosal healing (unstudied)

- Maintenance of response to certolizumab pegol (A, adults; children, not studied)

- Maintenance of remission after certolizumab pegol (A, adults; children, not studied)

- Loss of response to infliximab (B)
  - Somewhat lower absolute response rates than in anti-TNF naïve patients

- Induction of response in outpatient adults with draining perianal fistulas has yet to be evaluated

- Steroid-sparing data have yet to be evaluated

- Extraintestinal manifestations of CD have yet to be evaluated
  - Spondyloarthropathy
  - Arthritis/arthralgia
  - Pyoderma gangrenosum
  - Uveitis

**Certolizumab pegol in UC.** Insufficient data currently support the use of certolizumab pegol in the treatment of UC.

**Certolizumab pegol dosing in CD.**

- Recommended dosing is 400 mg SC at weeks 0, 2, and 4.
  - No evidence of benefit for additional treatment in week 6 nonresponders

- Patients who respond to the induction regimen should continue on maintenance dosing with 400 mg SC every 4 weeks.
  - Additional dosing schedules have not been evaluated in IBD but anticipate similar recommendations to other anti-TNFs regarding higher dose/reduced interval treatment. In patients with rheumatoid arthritis, changing the maintenance dosing schedule to 200 mg SC every 2 weeks increases drug exposure by approximately 50%.

**Contraindications to anti-TNF therapy.** Contraindications to anti-TNF therapy are consistent across the class. The panel notes the following contraindications:

- Known hypersensitivity to agent, if severe
- Active infection
- Untreated latent tuberculosis
- Preexisting demyelinating disorder
- Moderate to severe congestive heart failure
- Current or recent malignancy, without advice from an oncologist
- Further treatment with infliximab is contraindicated when the patient presents with uncontrolled infusion reactions.
- Any anti-TNF should be discontinued when there is no response to induction therapy or when the duration of response decreases to an economically im-
practical time frame (less than 1 week with adalimumab, 2 weeks for certolizumab, or less than 4 weeks with infliximab).

**Natalizumab (Tysabri).** *Indications for natalizumab in CD, including anticipated proposed restrictive labeling.* Given recent reports of PML from reactivation of the latent JC polyoma virus in association with natalizumab, its reintroduction into clinical practice for the treatment of multiple sclerosis was accompanied by restrictive labeling. Natalizumab is currently under regulatory review in North America and Europe. Assuming that it receives regulatory approval for the treatment of CD, it is likely to have restrictive labeling for this indication as well. Natalizumab is indicated for the induction and maintenance of response or remission in patients with moderate to severely active CD with documented inflammation, such as an elevated CRP concentration. Patients must be informed of the possibility of PML.

Because of the risk of PML, the use of natalizumab should be confined to patients who are refractory to or intolerant of an adequate trial of immunomodulator therapy and anti-TNF therapy and for whom surgery is not an acceptable option.

In addition, because of the risk of PML, natalizumab should not be used concomitantly with other noncorticosteroid immunomodulators or biologic immunosuppressive agents and, as with all biologic agents discussed, the intention for treatment is that successful therapy implies that corticosteroids should be tapered and discontinued.

- **Induction of response**
  - In adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates or antibiotics or corticosteroids, immunomodulators, or anti-TNF (A, adults; C, children)

- **Induction of response and remission to natalizumab documented only in patients with elevated CRP concentration**
  - Panel concludes natalizumab is appropriate only for patients with documented active inflammation

- **Induction of remission**
  - In adults and children who are outpatients with moderately to severely active disease and elevated CRP concentration who have failed therapy with and are treated concomitantly with aminosalicylates or antibiotics or corticosteroids, immunomodulators, or anti-TNF (A, adults; C, children)
  - Mucosal healing (unstudied)

- **Maintenance of response to natalizumab (A, adults; C, children)**

- **Maintenance of remission after natalizumab (A, adults; C, children)**

- **Loss of response to infliximab (D)**

- **Steroid sparing (B)**

- **Extraintestinal manifestations of CD (unstudied)**
  - Spondyloarthropathy
  - Arthritis/arthralgia
  - Pyoderma gangrenosum
  - Uveitis

**Natalizumab dosing.**

- Recommended dosing is 300 mg intravenously given at weeks 0, 4, and 8.

- Patients who respond to induction dosing should continue maintenance dosing with 300 mg intravenously given every 4 weeks.

- Other dosing regimens have not been adequately evaluated.

**Contraindications to natalizumab.**

- Known hypersensitivity to agent, if severe

- Active infection

- Current or past PML

**Other biologics.** Currently, insufficient data exist to recommend the following agents for clinical use in IBD: monoclonal antibodies to interleukin-12 (ABT-874, CNTO 1275), monoclonal antibodies to interferon gamma (fontolizumab), monoclonal antibodies to interleukin-6 receptors (tocilizumab), monoclonal antibodies to \( \alpha_4 \beta_7 \) integrins (MLN-02), antibodies to CD3 (visilizumab), antibodies to interleukin-2 receptor (basiliximab, daclizumab), antisense molecules for intercellular adhesion molecule 1 (alicaforsen), CTLA-4Ig, a fully human recombinant fusion protein categorized as a costimulatory or second-signal blocker of T-cell activation (abatacept), and granulocyte-macrophage colony-stimulating factor (sargramostim).

**Consensus Panel Statements**

**What Are the Current Indications and Contraindications for Biologic Therapy in Inflammatory Bowel Disease?**

**Background.** Crohn’s disease (CD) and ulcerative colitis (UC) are chronic, frequently disabling diseases that affect approximately 1 million people in both the United States and Europe. They are characterized by a remitting and relapsing course that despite current treatment ultimately progresses. Patients with CD commonly require surgery, with approximately 20% requiring surgery within 3 years of diagnosis and as many as 70% undergoing surgery at 15 years.\(^3\) CD and UC cause serious deterioration in quality of life; in one study, many patients re-
ported quality-of-life impairments similar to those experienced by patients with class III/IV heart failure. Many patients are unable to work, and given the young onset of inflammatory bowel disease (IBD), many years of productivity are lost. Furthermore, traditional therapies, such as glucocorticosteroids, when used chronically, result in a broad range of well-described morbidities. Thus, in recent years significant attention has been paid to the development of new, potentially more effective, less toxic and disease-modifying therapies.

The introduction of “biologic therapy” or “biologics” into the IBD armamentarium over recent years has greatly changed therapy, particularly for patients with refractory or corticosteroid-dependent disease. Biologic therapy, as defined by the Food and Drug Administration’s Center for Biologics Evaluation and Research, are agents that in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Most biologics are complex mixtures that are not easily identified or characterized, and many biologics are manufactured using biotechnology. Biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available.

Biologic agents include native biologic preparations and isolates, recombinant peptides or proteins (including cytokines), antibody-based therapies, nucleic acid-based therapies (antisense oligonucleotides), and somatic gene therapies that are agents targeted against specific mechanisms of disease.

With respect to IBD, while many such therapies are under investigation, the only therapies to date that have been approved or are in an imminent review process are monoclonal antibodies or antibody fragments. In contrast, immunomodulatory therapy connotes conventional therapies that also impact on some aspect of the immune response, such as 6-mercaptopurine, azathioprine, and methotrexate. For the purposes of this report, the term “biologics” refers only to antibody-based therapy.

The era of biologic therapy in IBD was ushered in by infliximab, initially indicated for CD. Infliximab is a chimeric immunoglobulin (Ig) G1 monoclonal antibody targeted against tumor necrosis factor (TNF). TNF is a proinflammatory cytokine with a wide range of effects, including up-regulation of adhesion molecules responsible for local recruitment of circulating lymphocytes, induction of matrix metalloproteinases found in the lamina propria, activation of additional proinflammatory pathways, and formation of granuloma.

Infliximab has proven efficacy for the treatment of refractory and fistulizing CD. In the wake of its success, other anti-TNF therapies have been evaluated, including adalimumab and certolizumab pegol, and newer approaches targeting other inflammatory pathways have emerged, including selective adhesion molecule inhibition (eg, natalizumab), interleukin-12 monoclonal antibodies, interferon gamma antibodies, and more (Table 3). Furthermore, data from other diseases and data now beginning to accumulate from IBD research indicate that biologics, or at least anti-TNF strategies, may not only treat the symptoms but also may modify the natural course of disease. The enthusiasm for broader adoption and earlier use of biologics has been tempered, however,

### Table 3. Biologic Agents in IBD by Target

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Currently approved for CD</th>
<th>Currently approved for UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticytokine biologics</td>
<td>Anti-TNF</td>
<td>Infliximab (Remicade)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adalimumab (Humira)</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td>Certolizumab pegol (Cimzia)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Anti-α4 integrin</td>
<td>Natalizumab (Tysabri)</td>
<td>No</td>
</tr>
<tr>
<td>Antiselective adhesion molecule</td>
<td>Anti-αβ7 integrin</td>
<td>MLN-02</td>
<td>No</td>
</tr>
<tr>
<td>Other anticytokine biologics</td>
<td>Anti-IL-12</td>
<td>ABT-874</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Anti-interferon gamma</td>
<td>Fontolizumab</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Anti-interleukin-6 receptor</td>
<td>Tocilizumab (Actemra)</td>
<td>No</td>
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<tr>
<td></td>
<td>Anti-CD3</td>
<td>Visilizumab (Nuvion)</td>
<td>No</td>
</tr>
<tr>
<td>T-cell activation/differentiation</td>
<td>Anti-interleukin-2 receptor</td>
<td>Basiliximab (Simillect)</td>
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<td></td>
<td></td>
<td>Daclizumab (Zenapax)</td>
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<tr>
<td></td>
<td>CTLA-4Ig</td>
<td>Abatacept (Orencia)</td>
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<tr>
<td>Stimulation of innate immune response</td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
<td>Sargramostim (Leukine)</td>
<td>No</td>
</tr>
</tbody>
</table>
with a growing recognition that their use can be associated with significant and sometimes fatal adverse consequences. Anti-TNF agents increase the risk of serious infections, including tuberculosis (TB) and other intracellular pathogens. More recently, reports concerning increased lymphoma risk, particularly the rare hepatosplenic T-cell lymphoma, have emerged.10 The monoclonal antibody to α4 integrin, natalizumab, has recently been associated with the development of a rare but devastating neurologic condition, progressive multifocal leukoencephalopathy (PML).11

The serious potential consequences of biologic therapy, coupled with the significant costs of these agents, have occasioned closer scrutiny of their risks and benefits and raised questions about their appropriate role in IBD care. The IBD Biologics Consensus Panel has attempted to answer these questions.

**Indications for biologics in IBD: overview.** Many factors determine whether a medication is appropriate for a specific patient. Foremost among these are efficacy, safety, and tolerability. Secondary considerations include cost, convenience, and speed of response. Some biologics for IBD require intravenous (IV) infusion, while others are administered subcutaneously by health care professionals or patients themselves.

Immunogenicity, in both the short term and long term, may vary by agent and also merits consideration. Other practical factors also drive use, including regulatory approval (ie, labeling) by governmental agencies such as the FDA in the United States and the European Agency for the Evaluation of Medicinal Products, “restricted use” programs, enforced by pharmaceutical companies themselves (such as with the reintroduction of natalizumab for the treatment of patients with multiple sclerosis and, potentially in the near future, of patients with CD), physician and staff familiarity, and willingness of governments, private insurers, or patients to pay or reimburse for use. Clinical evidence in scientific publications may also support off-label use.

When weighing the risks and benefits of biologic therapy for patients with IBD, physicians must account for the consequences of undertreated IBD. These include the direct costs of hospitalizations and operations for IBD, the direct costs of treatment for side effects associated with chronic, nonbiologic therapies, and indirect costs associated with lost productivity or nonmonetary costs such as quality-of-life decrements.

**Indications for biologic therapy in CD.** The need for biologic therapy is determined by disease activity, complications, and response to prior therapy. As noted in the American College of Gastroenterology 2001 CD practice guideline, biologic therapy is generally considered when CD is moderately to severely active despite concomitant therapy with aminosalicylates, corticosteroids, and/or immunomodulators or if corticosteroids or immunomodulators are contraindicated, not tolerated, or ineffective.12 Biologic therapy may also be indicated if patients with CD are corticosteroid dependent or refractory to glucocorticoids and/or immunomodulator treatment or to previous treatment with other biologics. Patients with complications such as draining fistulas or extraintestinal manifestations may derive particular benefit from biologic therapy.

**Goals of biologic therapy in CD.** Treatment goals include induction and maintenance of clinical remissions, induction and maintenance of closure of draining fistulas, mucosal healing, and steroid sparing. Ideally, successful therapy yields corticosteroid-free remission; however, in reality, especially among severely ill or treatment-refractory patients, therapeutic success may encompass varying degrees of efficacy, including corticosteroid reduction, or response without frank remission. Ultimately, physicians and patients must define adequate response to biologic therapy in individual patient scenarios.

**Indications for biologic therapy in UC.** Similar indications drive the use of biologic therapy in UC, including mild to moderate disease activity in the setting of corticosteroid dependence, severely active, corticosteroid-dependent disease, or disease refractory to glucocorticoids or immunomodulator treatment.

**Goals of biologic therapy in UC.** The goals of biologic therapy in UC are similar to those in CD and include induction of corticosteroid-free remission, maintenance of remission, mucosal healing, and a steroid-sparing effect. As in CD, the degree of response that is considered success may vary; however, in UC, for which colectomy is an effective and acceptable treatment, continued use of biologics in the face of partial response must be carefully evaluated.

**Specific indications for infliximab.** Indications in CD. Infliximab is a chimeric mouse-human monoclonal IgG1 antibody that was the first FDA-approved biologic therapy for CD. The exact mechanism of action for infliximab is not known. Infliximab not only neutralizes circulating and membrane-bound TNF but also lyses activated T cells and macrophages and induces T-cell apoptosis.13

The ability of infliximab to induce remission in patients with refractory CD was shown in a small phase 2 randomized, double-blind, placebo-controlled trial in 108 patients reported by Targan et al in 1997.14 Patients received a single infliximab infusion of 5 mg/kg, 10 mg/kg, or 20 mg/kg or placebo. After 4 weeks, 81% of patients receiving 5 mg/kg demonstrated a significant clinical response, defined as a reduction of ≥70 points in the Crohn’s Disease Activity Index (CDAI), compared with 17% response among those who received placebo. Subsequent longer-term randomized studies have shown its ability to maintain remission. The ACCENT I trial, a larger, randomized trial of infliximab maintenance, showed that among patients who had responded (reduc-
Infliximab has been particularly useful in the treatment of patients with corticosteroid-dependent and fistulizing disease. In the ACCENT I trial, among week 2 responders who required corticosteroids at baseline, 24% of those maintained on infliximab every 8 weeks at 5 mg/kg and 32% of those receiving 10 mg/kg were in corticosteroid-free clinical remission at week 54. Only 9% of patients receiving placebo maintained corticosteroid-free remission.15

Among patients with CD-related enterocutaneous (largely perianal) fistulas, Present et al reported that infliximab induced complete cessation of drainage from fistulas in 55% of patients receiving 5 mg/kg infliximab maintenance infusions, compared with a placebo response rate of 13%.16 Data from the ACCENT II trial showed similar results; among infliximab responders, 73% had complete fistula response at week 10, and at week 54, 36% of patients in the 5 mg/kg infliximab maintenance group had continued complete absence of draining fistula compared with 19% of patients maintained on placebo.17 Studies indicate that successful infliximab-induced fistula closure varies by location, with as many as 93% of perianal fistulas resolving.18

**Indications in pediatric patients.** Among pediatric patients, the REACH (Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF alpha Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe Crohn’s Disease) study evaluated the safety and efficacy of infliximab in pediatric patients aged 6–17 years with moderate to severe CD who were on immunomodulator therapy and infliximab naïve.19 Week 10 response and remission rates following a 3-dose infliximab induction regimen were higher than those found among adults in the ACCENT I trial and reached nearly 90% and 60%, respectively. Maintenance dosing at 8-week intervals maintained response (64%) and remission (56%) at 54 weeks. The response and remission rates were significantly better with infusions every 8 weeks than with infusions every 12 weeks.

**Indications in UC.** The ACT-1 (Active Ulcerative Colitis Trial) study was a randomized placebo-controlled trial that showed the efficacy of infliximab to induce response (primary end point) and remission among outpatients with UC.20 Significantly greater numbers of patients receiving infliximab than placebo achieved clinical response or remission. Among those treated with infliximab 5 mg/kg, 69% achieved clinical response and 39% achieved clinical remission by week 8. Of those receiving 10 mg/kg, 62% achieved clinical response at week 8 and 32% achieved clinical remission at week 8. In contrast, only 37% and 15% of patients randomized to placebo achieved a response or remission during the same period. Clinical responses and remissions were generally maintained through week 30 and, in the ACT-1 study, through 54 weeks. Of patients who received infliximab 5 mg/kg, 52% maintained response and 34% maintained remission at week 30, rates significantly higher than those among placebo-treated patients.20 Infliximab treatment also correlated with significant differences in the proportion of patients who experienced mucosal healing, defined as an endoscopic subscore of 0 or 1, at weeks 8, 30, and 54. The ACT-2 study, which was of identical design but also included outpatients refractory to aminosalicylate therapy and continued for only 30 weeks, showed similar results. Infliximab (5 mg/kg) treatment resulted in 47% response, 26% remission, and 46% mucosal healing at week 30.20

Infliximab can facilitate corticosteroid withdrawal in UC. In the ACT-1 trial, 24% of patients taking 5 mg/kg successfully discontinued corticosteroids at week 30, a rate more than twice that of those taking placebo.20 Similar results were seen in the ACT-2 study, where among those treated with infliximab 5 mg/kg, the corticosteroid discontinuation rate was 18%, compared with a rate of only 3% among those not receiving active drug.20 Infliximab may serve as rescue therapy among those with severe UC. In a study among hospitalized patients with UC experiencing acute severe UC unresponsive to IV betamethasone, those randomized to receive infliximab had significantly lower colectomy rates at 90 days (29%) in contrast to a surgery rate of 67% among those receiving placebo.21

**Adalimumab.** Adalimumab in CD. Adalimumab is a recombinant fully human IgG1 monoclonal antibody that binds TNF and, similar to infliximab, induces T-cell apoptosis. In the Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease (CLASSIC) trial, patients who were anti-TNF naïve experienced significant response and remission rates when given adalimumab subcutaneously (160/80 mg) at an interval of 2 weeks.26 Clinical response (defined as a decrease in CDAI of at least 100 points) occurred in 50%, and 36% experienced clinical remission (defined as a CDAI of ≤150 points).
The CHARM (Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance) study was a maintenance trial of adalimumab and enrolled both those who had been previously treated with anti-TNF therapy as well as anti-TNF naïve patients.27 CHARM showed that adalimumab, when given every other week to adalimumab responders, can maintain remission. At week 56, among anti-TNF naïve patients, 48% were in remission, in contrast to 34% of patients who had been previously exposed to anti-TNF therapy. Additionally, adalimumab resulted in higher rates of corticosteroid-free remission and fistula closure at 56 weeks.27

The GAIN trial (Gauging Adalimumab effectiveness in Infliximab Non-Responders) showed that, among patients with moderately to severely active CD who were intolerant of or unresponsive to infliximab, 3 times as many patients who received adalimumab achieved clinical remission, defined as a CDAI of <150 points at week 4, compared with placebo.28 Adalimumab has not been studied, specifically in fistulizing CD, in children or among patients with UC.

**Certolizumab pegol.** Certolizumab pegol is a pegylated Fab fragment of an anti-TNF monoclonal antibody. It does not have an IgG component and appears to function without causing T-cell apoptosis.29,30

The PRECiSE 1 (Pegylated antibody fRagment Evaluation in Crohn’s disease) study, which was presented in 2006, was a stratified randomized evaluation of certolizumab pegol as induction therapy for patients with moderate to severe CD, defined as a CDAI of 220–450.31 Subjects were stratified before treatment based on C-reactive protein (CRP) level <10 mg/L or ≥10 mg/L and baseline use of corticosteroids and/or immunosuppressants. Response rates were significantly better for certolizumab pegol-treated patients than placebo-treated patients at weeks 6 and 26, regardless of baseline CRP levels.

The PRECiSE 2 trial, using similar enrollment criteria and stratification, evaluated the efficacy of certolizumab pegol to maintain remission among certolizumab pegol responders.32 During the open-label induction phase, patients received certolizumab pegol 400 mg subcutaneously at weeks 0, 2, and 4. Responders, defined as those with at least a 100-point decrease in CDAI score (64.1%), were randomized in a double-blind manner at 6 weeks to receive certolizumab pegol or placebo maintenance injections every 4 weeks. Maintenance of response occurred in 62.8% at week 26 among the overall population as compared with 36.2% for placebo. Week 26 remission rates, defined as a CDAI score ≤150, were 47.9% among the overall intention-to-treat group compared with 28.6% in the placebo group.

Certolizumab pegol has not yet been evaluated in fistulizing CD, as a corticosteroid-sparing agent, in UC, or in children with IBD.

**Natalizumab.** Natalizumab is a humanized monoclonal antibody targeted against α4β1 and α4β7 integrins. The integrins are glycoprotein receptors found on cell surfaces of lymphocytes that facilitate the migration and activation of T cells.

In a double-blind, placebo-controlled phase 2 trial, Ghosh et al reported that among patients with moderately active CD, those who received higher doses of natalizumab (6 mg/kg at weeks 0 and 4) had significantly better remission rates than placebo at week 4 (29% vs 14%) and week 8 (43% vs 16%).33 However, at the prospectively identified study end point, week 6, no significant differences emerged between those treated with placebo or active drug. Following this trial, a large phase 3 study of natalizumab for induction and maintenance treatment, ENACT-1 (Efficacy of Natalizumab as Active Crohn’s Therapy), commenced.34 At the prespecified time point of week 10, natalizumab was not significantly more effective than placebo; however, a statistically significant response was observed at week 12. A higher proportion of patients in the natalizumab group achieved a clinical response compared with those in the placebo group throughout the study, although the differences were not statistically significant (of note, the lack of significance may relate to the high placebo response, which approached 50% throughout much of study). A subsequent study, ENCORE (Efficacy of Natalizumab in Crohn’s disease Response and rEmission), showed that among patients with elevated CRP levels, natalizumab was superior to placebo in induction of response and remission at all time points.35

The ENACT-2 study showed that natalizumab effectively maintains remission.34 In this study, initial responders were randomized to receive a maintenance regimen of either placebo or natalizumab once monthly. Patients who received active drug experienced significantly better remission rates at 6 months than those receiving placebo (44% vs 26%); furthermore, natalizumab induced response in 54% of patients previously treated with anti-TNF therapy compared with 15% of placebo-treated patients. Steroid-sparing benefits were also shown. Among those patients who attained sustained remission with natalizumab therapy, 42% were withdrawn from oral corticosteroid therapy at 60 weeks compared with 15% in the placebo-treated group.34

The study and marketing of natalizumab were voluntarily suspended in February 2005 due to 3 reports of JC polyoma virus–related PML among natalizumab-treated patients, 2 with multiple sclerosis36,37 and one with CD.38 Subsequent worldwide safety evaluation revealed no further cases of PML, yielding an incidence of approximately 0.1%; however, therapy had been stopped in all patients.39

Given this development, patients must be informed of the possibility of PML. Furthermore, proposed restrictive labeling will limit the use of natalizumab to patients who are refractory to or intolerant of an adequate trial of immunomodulator therapy and anti-TNF therapy and for whom surgery is not an acceptable option. In addi-
tion, because of the risk of PML, natalizumab should not be used concomitantly with other noncorticosteroid immunomodulators or biologic immunosuppressive agents.

**Combination biologic therapy.** There appear to be many effectors of abnormal immune activity in IBD. In theory, suppression of multiple pathways should allow better disease suppression but would be anticipated to incur more adverse reactions, especially infections. In a phase 2 study, Sands et al randomized adult patients with active CD (CDAI ≥150) despite ongoing infliximab therapy to receive either 3 natalizumab or placebo infusions. At week 10, 42.3% of patients receiving both drugs had a clinical response, compared with 29.6% of patients taking infliximab alone. Clinical response seemed durable; 25% of patients in the natalizumab and infliximab group met the criteria for response at all time points from week 6 to week 10, compared with 11% of patients taking infliximab alone. At week 10, 36.5% of patients taking combined therapy achieved clinical remission, compared with 29.6% of patients receiving infliximab alone. The rates of adverse events, and notably of serious adverse events, were similar between treatment groups. These results were not statistically significant and do not support the clinical use of combined biologic therapies at this time. These findings do, however, suggest that an adequately powered study is warranted to further explore such regimens, particularly among the most refractory patients.

**What Are the Appropriate End Points for Clinical Trials of Biologic Therapy in IBD?**

**For individual patients.** When evaluating IBD therapies, a range of outcomes has been used. Those of relevance to a clinician and his or her patient may be substantially different from those of relevance in clinical trials. In the treatment of individuals with IBD, the optimal treatment outcome is corticosteroid-free remission. In reality, treatment success is often defined in less absolute terms.

Symptomatic improvement is the major determinant of therapeutic success for patients with IBD. The role of other measures, such as endoscopy, is unclear. Endoscopy is generally performed before initiating new treatment for CD or UC to verify disease activity and to exclude other causes of symptoms, such as concurrent infection. In UC, endoscopic healing correlates well with overall disease improvement and flexible sigmoidoscopy may provide a useful follow-up tool in the clinical setting. The usefulness of endoscopic results after treatment of CD has begun is undocumented. Data suggest that mucosal healing correlates with other important end points in clinical trials; however, the relationship of mucosal healing and symptomatic response for individual patients has not been studied. Conversely, no data provide guidance regarding continued treatment when patients have symptomatic improvement in the absence of mucosal healing.

**For clinical trials.** Careful scrutiny of the design and end points of clinical trials provides a basis to attempt to compare biologic agents with each other, and with other therapies. A range of outcomes measures has been used in IBD research, reflecting aspects of disease of varying importance to clinicians, researchers, and patients. These include disease activity indices (eg, CDAI), physiologic surrogates (eg, CRP), quality-of-life scores (eg, IBQ Questionnaire), endoscopic scores (Crohn’s Disease Endoscopic Index of Severity), economic measures (eg, quality-adjusted life years), and rates of complications, hospitalization, surgery, and mortality.

The interpretation of clinical trials in IBD is complicated by varying measures of remission and response. Remission may be defined as the absence of inflammatory signs and symptoms, prevention of postoperative recurrence, or normalized quality of life. In CD, remission can include fistula closure or CDAI <150 with evidence of mucosal healing. In UC, the absence of rectal bleeding, normal stool frequency, and mucosal healing are measures of remission. By implication, remission should be corticosteroid free and reports of clinical trials should be transparent in describing the effect of treatment at achieving corticosteroid-free remission.

Response is a substantially less robust or desirable end point and may include reduction of signs and symptoms or prolongation of postoperative remission. Specific definitions of response in CD include a CDAI reduction of 100 or 70 points or a reduction in number or degree of fistula drainage. In patients with UC, response may include reduction in bleeding and stool frequency. A reduction in corticosteroid requirement (“steroid sparing”) is regarded as the least acceptable measure of treatment efficacy.

Ideally, the outcome measures selected need to be responsive to clinically meaningful changes and reliable and not subject to change in the face of unchanged disease activity. This is especially necessary in IBD research because spontaneous remission is common and placebo response rates can be high. Placebo response rates in CD trials (when defined as a CDAI reduction of at least 70 points) commonly exceed 30% and have been as high as 51%. These high placebo rates may reflect the natural history of disease, the phenomenon of regression to the mean, the influence of more frequent contact with health care providers, and the use of concomitant medications, which commonly occurs in clinical IBD trials. Data indicate that placebo response is inversely proportional to study duration and entry CDAI. It is useful to recall that some end points, such as hospitalization rates, may reflect practice patterns more than disease state.

As new research focuses on the ability of therapy to modify early or preclinical disease, the ability to measure treatment effects accurately becomes increasingly important and increasingly challenging. The ability to measure
and compare long-term outcomes will gain increasing importance, making the development of long-term outcome indices a clinical research priority.

**Specific outcomes measures in CD.** In CD research, disease activity indices include the CDAI, Harvey–Bradshaw index, Organisation Mondiale de Gastroenterologie index, Cape Town index, van Hees or Dutch index, and the Therapeutic Goals score (Present/Korelitz index). Of these, the CDAI is most commonly used. The CDAI is a composite score including 8 subjective and objective criteria such as number of liquid stool daily, sense of well-being, hematocrit, and body weight. A higher score reflects more severe disease; the maximum score is 600. Remission is generally defined as a CDAI of ≤150, whereas response has been variably defined as a reduction in total score of between 70 and 100 points. Sands et al analyzed multiple budesonide induction trials and determined that remission defined as a CDAI <150 and response defined as a 100-point reduction in CDAI were the most efficient criteria. The issues around measurement of disease activity in clinical trials in patients with CD have been extensively reviewed elsewhere.

Physiologic markers, particularly CRP, are frequently measured in IBD trials. CRP plays an important role in the innate immune system. Its role in measuring IBD outcomes, however, is unclear. In their analysis of CD induction and maintenance trials, Will et al showed that CRP was an independent predictor of response to treatment. However, in contrast to the post hoc analyses suggesting that patients with an elevated CRP level had a greater response versus placebo than patients with low or normal CRP levels, patients randomized prospectively based on normal or high CRP levels in the PRECISE 2 trial of certolizumab pegol did not show any differential response. Nevertheless, CRP levels may inversely correlate with placebo response to biologic agents and trial efficiency may be increased by excluding patients with low CRP levels. This raises unanswered questions about the generalizability of results in different patient populations and highlights the critical role that the choice of CRP “cutoff” point might play in trial results.

The role of instruments such as the Crohn’s Disease Endoscopic Index of Severity, Simplified Endoscopic Index CD-SES, and Rutgeerts score to measure endoscopic improvement and mucosal healing in CD is unclear. The severity of endoscopically identified lesions does correlate to the likelihood of undergoing colectomy. These measures, however, may be cumbersome to use.

**Outcomes measures in UC.** The Powell–Tuck Index is a 20-point clinical index that includes subjective and objective measures such as well-being, abdominal pain, bowel movement frequency, stool consistency, bleeding, anorexia, nausea or vomiting, abdominal tenderness, complications (eye, joint, mouth, skin), and temperature. The Clinical Activity Index also incorporates both subjective and objective measures and includes the physician’s subjective assessment of the patient’s disease activity. The Mayo Scoring System, although not validated, has been widely adopted by regulatory agencies. It assesses 4 components of UC activity: stool frequency, rectal bleeding, endoscopic findings, and physician’s global assessment, each scored on a 0–3 scale. The Baron score rates the mucosal appearance on a 0–4 scale. Such endoscopic measures have emerged as relatively robust outcomes measures in UC, although interobserver variation in scoring of endoscopic appearance at flexible sigmoidoscopy remains to be validated. The issues around measurement of disease activity in clinical trials in patients with CD have been extensively reviewed elsewhere.

In trials of severe UC, typical outcomes measures include colectomy rates, endoscopy findings, and clinical disease activity indices. The Seo index incorporates the presence of clinical factors, such as blood in the stool and stool frequency, with laboratory findings, including the sedimentation rate, hemoglobin level, and albumin level, to calculate a value. A value <150 corresponds to remission or mild UC, 150–220 to moderately severe UC, and >220 to severe UC. Practical indices, such as the Sweden index, calculated on the third day after starting IV corticosteroids, factor CRP level and the number of daily bowel movements to predict the likelihood of colectomy. A total of 85% of patients with a CRP level >45 mg/L and a stool frequency of 3–8/day (Oxford index) undergo colectomy, or more than 70% of patients with a score >8 (stool frequency × 0.14 CRP ≥8 on day 3; Sweden index) undergo colectomy.

**Conclusions.** A range of outcomes measures exists in IBD clinical trials. CDAI remains the outcome measure of choice in CD trials. The role of CRP remains unclear related to individual patients, but in clinical trials patients with elevated CRP levels have greater relative response to therapy compared with placebo (eg, patients with low CRP levels have higher placebo response rates). Endoscopic measures have improved and may play a role in future CD trials. In UC, endoscopy affords a robust measure of outcome. In clinical trials involving severe colitis, indices such as the Seo, Oxford, or Sweden play an important role.

**What Are the Predictors of Response?**

While biologic therapy represents a great advance in IBD care, as many as 30% of patients remain refractory to treatment. Potential adverse effects, costs, and the increasing number of these agents provide motivation to identify predictors of response that would enable clinicians to target therapy to patients most likely to benefit. Investigators have explored the relationships between many epidemiologic, clinical, and pathophysiologic factors and response to biologic therapy. Given its status as the first biologic agent approved for use in IBD, and its initial indication in CD, the focus of this work has been
the relationship between CD and response to infliximab. Data regarding predictors of response in UC are premature but are the subject of intense research.

Predictors of response fall into 3 categories: clinical predictors, genetic predictors, and biochemical, serologic, and immunologic predictors. Among clinical predictors, a number of studies have shown that patients with disease of shorter duration have better response rates.19,65,66 Lionetti et al reported that among patients with fistulizing CD of less than 1-year duration, 83% had complete fistula closure compared with only 29% of those with disease of longer duration.65 In a small study of patients who were refractory to medical therapy, those patients with early CD had a longer relapse-free remission after a single infusion of infliximab compared with those with late disease.66 Patients with shorter duration of disease also had improved responses in the REACH, CHARM, and PRECISe 2 trials.19,67,68

Among patients with CD, disease behavior also correlates with response. Those with colonic disease, nonstricturing disease, or less severe disease are more likely to respond to infliximab.69,70 The differences in response rates can be substantial. Lichtenstein et al reported that among infliximab-treated patients, those with nonstricturing disease had a 94% response rate compared with a response rate of 47% among patients entering trials for strictureing disease.69 Response may also occur sooner among those without strictures. Laharie et al reported response rates of 96.5% at 2 weeks among those whose disease was characterized as inflammatory, compared with 73% among those with stenosing disease.70 Non-smokers fare better as well, with significantly higher response rates in both luminal and fistulizing disease.69–72

Previous and concurrent medical therapy also affect response. Maini et al showed that the duration of infliximab benefit was improved with concomitant use of methotrexate in patients with rheumatoid arthritis.73 Similarly, other cohort studies have shown that concomitant administration of immune suppression enhances the effects of biologics.71,72,74 The mechanism of this effect, however, is unclear. Concomitant use of infliximab and immune suppression may synergistically affect the underlying disease process. Immune suppression may control the development of immunogenicity, thereby enhancing the effect of biologics. Conversely, the addition of infliximab may elevate the level of immune suppression. It has been clearly shown that concomitant use of immunosuppressants decreases the development of antibodies to infliximab.75 In turn, the development of antibodies to infliximab is inversely correlated with subsequent degree and duration of response to infliximab.75 Among patients taking azathioprine who respond to infliximab, 6-thioguanine nucleotide levels increase, suggesting increased absorption of azathioprine.76 Infliximab nonresponders show no such change in 6-thioguanine nucleotide levels. Previous exposure to anti-TNF therapy lowers the absolute response rates but does not “rule out” response to subsequent anti-TNF. There does not appear to be immunogenic “crossover” among infliximab, adalimumab, and certolizumab pegol in open-label trials or in the PRECISe, CHARM, or GAIN trials; however, overall response rates in PRECISe, CHARM, and GAIN were lower in patients with previous anti-TNF exposure.

A range of genetic factors has been associated with varying CD phenotypes, and attempts have been made to link these factors to therapeutic response. Thus far, no definitive links have emerged. Some data indicate that FcGR III α-158, FasL-843, caspase 9, and TUCAN Cys1077–81 may correlate with infliximab response; however, these remain unconfirmed. Many studies have confirmed no role for TNF, TNF-α, and NOD2/CARD15 variants in therapeutic effect.82–86

Among inflammatory markers, only CRP has been consistently correlated with response.31,32,34,87 As previously mentioned, CRP levels are inversely correlated with lower rates of placebo response and, thus, greater differences between active therapy and placebo. Thus, by identifying groups less likely to improve on placebo treatment, elevated CRP levels can increase the power to studies to detect infliximab response. In a few series, the serologic markers perinuclear antineutrophil cytoplasmic antibodies and speckled anti-neutrophil cytoplasmic antibody (sANCA) appear to influence response to infliximab,81,88 although none have been conclusively shown to predict response. Taylor et al reported that among patients with CD, treatment response and reduction in CDAI was inversely related to the presence of perinuclear antineutrophil cytoplasmic antibodies and anti-Saccharomyces cerevisiae antibodies (ASCA).82

In clinical practice, none of these factors are accurate enough to determine whether individual patients would benefit from infliximab or other biologic therapies. These associations, however, may provide insights into the mechanisms of IBD and lead to the development of specific, clinically useful predictors.

What Are the Mechanisms of and Approaches to Preventing Immunogenicity to Biologic Therapies for IBD?

Immunogenicity has emerged as a significant factor in both the efficacy and safety of biologic therapies. Much remains unanswered about the development and consequences of immunogenicity. The development of immune reactions against specific biologics correlates with decreased subsequent degree and duration of response and can provoke allergic reactions.89–92 Thus, immunogenicity, especially relative to specific biologics, has taken center stage in discussions about clinical use and in pharmaceutical marketing campaigns. Furthermore, the risk of developing immunogenicity and loss of response to an individual biologic agent must be bal-
anced against potential toxicities of combining biologics with immune suppressants to reduce immunogenicity.

“Antigenicity” is the ability of a molecule to be recognized by a preexisting T-cell receptor or a B-cell receptor (antibody). After an antigen is recognized by a receptor, it induces either tolerance or an immune response. The same antigen can induce different responses depending on factors such as mode of administration and uptake by and costimulation of antigen-presenting cells. Thus, immunogenicity of a biologic will vary by intrinsic patient factors and features of the drug and its administration. Structural features of drugs that have important effects on immunogenicity include murine constant regions, V-region sequences, human Ig allotypes, and the presence of unusual glycosylation. An agent’s mechanism of action also influences immunogenicity, including how specific an antibody is, whether it is bound to the cell surface or a soluble antigen, and whether it forms immune complexes, activates complement, or induces cytokine release. The method of administration (eg, subcutaneously vs IV), frequency of administration, dosage, and concomitant use of other medications greatly affect immunogenicity. Patient factors, such as disease status, immune status, and major histocompatibility complex haplotype, also modify the immune response.

“Humanness” (eg, chimeric, humanized, or fully human), often promoted as an important feature and presumed by some to be a determinant of immunogenicity, reflects how a biologic was made but does not reflect the final protein sequences. Functional humanness, or the degree to which a compound may potentially induce an immune response, relates to the degree of homology that an agent shares with some human proteins. Due to allelic variation in inheritance and expression of human germline V-gene, some patients may not have the V-genes used in humanized or fully human antibodies. Furthermore, investigation of mouse and human antibodies shows high levels of homology between the antibodies from these disparate species. Thus, a more “human” biologic may have less homology to human proteins than a chimeric, murine-based compound. Pharmaceutical companies may tout the “humanness” of products without providing data on the sequence of biologics. While the latter may help protect proprietary information, it impedes comparative analysis of immunogenicity.

The interpretation of the ability of a specific agent to induce an immune response is hampered by the lack of a consistent approach. While study data clearly indicate the presence or absence of antibody, further conclusions are difficult. Different studies have used different assay formats with different sensitivities and cutoffs; thus, determining absolute frequency of immune responses and comparing agents is problematic.

How then should immunogenicity be determined and compared between agents? Successful action against the target cytokine, TNF, should lead to reduced circulating levels. Conversely, if the body has mounted a significant immune response against a biologic, the circulating levels of that biologic will be reduced. Based on these mechanisms, measurement of biologic and TNF levels can provide insight into immunogenicity. These assays are applicable to all the biologics and seem to be highly indicative of patient immune responses for infliximab.

The formulation and administration of biologics can yield less immunogenic agents. Soluble antibodies are less immunogenic than cell surface–bound antibodies, and it appears that IV agents may be less immunogenic than those administered subcutaneously.

A number of approaches have been shown in clinical practice to reduce immunogenicity. Concomitant immune suppression with azathioprine has been correlated with decreased immunogenicity in IBD studies. Studies in the rheumatoid arthritis population indicate that low-dose methotrexate is effective at reducing immunogenicity, although its use in IBD remains relatively unexplored.

Episodic reinfusion increases immunogenicity compared with a regular maintenance schedule. Conversely, maintenance of consistent plasma concentration of biologics decreases immunogenicity. Generally, this has been achieved through more frequent, scheduled dosing, in contrast to a single infusion or episodic therapy. Using high doses of antibody also correlates with better tolerance; it is unclear whether this reflects induction of tolerance or increased immunosuppression by the biologic.

All biologic therapies have the potential to induce immunogenicity. Homology reduces antigenicity, but “humanization” does not equate with homology and human antibodies may be immunogenic. While appropriate selection of sequences of antibody constant and variable regions will reduce immunogenicity, other factors outside of biologic design will continue to drive aspects of tolerance and immunogenicity.

Given that immune responses are possible with all biologics, including those that have a fully human sequence (eg, erythropoietin, interferon beta, and so on), all clinical trials should include measurements of patient immune responses. Measurement of drug concentrations is a preferred measure of a biologic response and directly correlates with drug efficacy. All studies should adopt these measures and make results freely available to the scientific community.

In practice, high dose induction with concomitant immune suppression, followed by continuous maintenance therapy, reduces immunogenicity. However, once therapy has been interrupted, reinduction therapy should be considered with great caution due to the risk of inducing a rapid anamnestic response, in particular with IV administration (eg, infliximab). Pretreatment with corticosteroids is advocated in this situation, and patients should be educated regarding the risk of acute or delayed hypersensitivity reaction, in particular to a second influ-
sion. Similarly, with episodic therapy, corticosteroids may be advocated before infliximab infusions to reduce acute or delayed infusion reactions or in some selected cases to reduce immunogenicity when, for example, concomitant immune suppression is not administered.

**What Are the Comparative Efficacies of Biologic Agents in IBD?**

Since the successful introduction of infliximab for CD, numerous biologic agents have been developed for use in both CD and UC. Thus, great efforts have been made to understand their relative efficacies and risks.

When comparing currently available biologics for IBD, their relative structures (Table 4) and mechanisms of action often receive significant attention and form the basis for inferences about relative immunogenicity. Such comparisons may be useful for research endeavors, but structural and functional characteristics do not uniformly correlate with efficacy or side effects. For example, infliximab, adalimumab, and, in some studies, etanercept have been shown to cause T-cell apoptosis; however, only infliximab and adalimumab effectively induce and maintain remission in CD. Placebo-controlled trials of etanercept (P75 receptor fusion protein) and oncept (P55 receptor) in moderate to severe CD failed to show efficacy. In contrast, certolizumab pegol has recently shown the ability to induce and maintain remission in CD despite its lack of effect on T-cell apoptosis.

Direct comparisons between biologics are limited by variations in study design and, in the case of UC, a limited number of studies (Table 5 and Figure 1). Short-term induction studies, including that by Targan et al of infliximab, CLASSIC I (adalimumab), natalizumab, ENACT-1 (natalizumab), ENCORE (natalizumab), certolizumab pegol, and PRECiSE I (certolizumab pegol), were designed using a placebo-controlled induction phase and early end point evaluation (at 4, 6, or 12 weeks). Patients were randomized to receive placebo or one of multiple doses of active drug, with primary end points of response (usually defined as 70-point or 100-point reduction in CDAI) and remission (CDAI <150). The initial multicenter, double-blind, placebo-controlled trial by Targan et al showed that a single dose of infliximab (5 mg/kg) was significantly more effective than placebo for producing a 4-week clinical response (≥70-point reduction in CDAI from baseline) and clinical remission (CDAI <150) in patients with moderate to severe, treatment-resistant CD. The subsequent studies, except ENACT-1, showed the ability of these anti-TNFs and natalizumab (ENCORE) to induce response and remission among patients with active CD. Despite showing significant benefits at other times (weeks 8 and 12), ENACT-1 failed to meet its prespecified study end point, response and remission at week 10. As previously mentioned, this finding may relate to the high placebo response and remission rates. At 4 and 12 weeks, the rates of response (51% and 61%, respectively) and remission (23% and 40%, respectively) were similar to those shown with infliximab 5 mg/kg (70-point CDAI reduction in 81% and remission in 48% at week 4), adalimumab 160/80 mg in CLASSIC (100-point CDAI reduction in 50% and remission in 36% at week 4), certolizumab pegol in PRECiSE 1 (100-point CDAI reduction in 33% and remission in 20% at week 4), and natalizumab in ENACT-1 (70-point CDAI reduction in 51.2% and remission in 17.9% at week 4) and ENCORE (70-point CDAI reduction in 51% and remission in 24% at week 4 among patients with CRP elevations at baseline).

Maintenance trials such as ACCENT I, CHARM, and PRECiSE 2 have consisted of open-label induction phases followed by randomization of responders to evaluate maintenance of response (70-point and 25% or 100-point reduction in CDAI) and remission (CDAI <150). The ACCENT I trial showed maintenance of clinical remission at week 54 in 28% and 38% of infliximab-treated patients (5 mg/kg and 10 mg/kg), respectively, compared with 14% among those given placebo. Adalimumab maintenance was evaluated in the CHARM trial using 2 primary end points: remission at 26 and 54 weeks. Among those taking adalimumab (40 mg) either weekly or every other week, 26-week remission rates were significantly better than placebo (40%, 47%, and 17%, respectively). Similar differences persisted at 54 weeks, with rates of remission at 36%, 31%, and 12%, respectively. In PRECiSE 2, among those in remission at 6 weeks, 47.9% remained in remission at 26 weeks compared with a placebo remission rate of 28.6%.

The PRECiSE I trial included both a double-blind, placebo-controlled induction and maintenance phase.

### Table 4. Characteristics of Anti-TNF Agents

<table>
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<tr>
<th>Mode of Action</th>
<th>Characteristics of anti-TNFα agents</th>
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<tr>
<td><strong>Agent</strong></td>
<td><strong>Tetrahydrobiopterin</strong></td>
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<tr>
<td>Infliximab</td>
<td>+</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>+</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>+</td>
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**Classic I (adalimumab)**, **natalizumab**, **term induction studies**, including that by Targan et al of CD despite its lack of effect on T-cell apoptosis.87,31,32,87
<table>
<thead>
<tr>
<th>Design</th>
<th>n</th>
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<th>Induction</th>
<th>Randomized dose</th>
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<th>Frequency of administration</th>
<th>Response needed for randomization</th>
<th>Primary outcome assessment time</th>
<th>Remission CDAI &lt;150</th>
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<th>Statistical significance</th>
<th>Remission CDAI and off corticosteroids</th>
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<th>Response 100-point remission</th>
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<td>Response CDAI &gt;70 at wk 4 (58%)</td>
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<td>Response CDAI &gt;70 at wk 4 (58%)</td>
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<td>24</td>
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<td>41</td>
<td>0.001</td>
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CD maintenance of remission

PRECISe 1 Steroid | 669 | Certolizumab | Placebo | None | 10 | wk 56 | Response CDAI >70 at wk 4 (58%) | 36 | 0.001 | 24 | 0.008 | 41 | 0.001 | 36 | 0.027 |
<table>
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<tr>
<th>Design</th>
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<th>Remission CDAI &lt;150</th>
<th>Statistical significance corticosteroids</th>
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<td>wk 26/CRP</td>
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<td>wk 26/CRP</td>
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<td></td>
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<td>Placebo</td>
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<td>Placebo</td>
<td>wk 56</td>
<td>Every 8 wk</td>
<td>17</td>
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<tr>
<td>ACT 2</td>
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<td>10</td>
<td>Placebo</td>
<td>wk 56</td>
<td>Every 8 wk</td>
<td>34</td>
<td>0.001</td>
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<td>Rutgeerts et al, 2005(26)</td>
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<td>wk 56</td>
<td>Every 8 wk</td>
<td>11</td>
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<td>wk 56</td>
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The primary end point was combined early and late response, defined as a 100-point reduction in CDAI. At week 6, a 35.2% response (100-point CDAI reduction) rate was seen; the combined 6- and 26-week rate was 23.1%. Among 6-week responders, maintenance of remission at 26 weeks was 14.4%. Data from the ENACT-2 trial indicate that natalizumab can maintain remission among those who respond to natalizumab induction; at week 60, 55% of patients receiving natalizumab were in remission compared with 22% of those receiving placebo.34 Other important measures of efficacy, such as corticosteroid withdrawal, and fistula closure appear similar between groups where data are available. In the ACCENT I trial, 31% of those treated with infliximab (5 mg/kg) and 37% of those treated with infliximab 10 mg/kg were corticosteroid free at week 30.17 At week 54, rates remained significantly better than placebo: 32% for the higher dose and 24% for the lower dose. Among adalimumab-treated patients, at 26 weeks, 30% of those taking 40 mg each week and 35% of those taking 40 mg every other week remained off corticosteroids.35 The ENACT-2 trial showed that at 15 months, 49% of natalizumab-treated patients were corticosteroid free compared with 20% in the placebo group.34 Corticosteroid withdrawal data from the PRECiSE trials have not been reported; therefore, it is unclear how certolizumab pegol compares in this regard.

Complete fistula closure occurred in 55% of infliximab-treated patients in the study by Present et al.16 Among patients treated with adalimumab (40 mg every other week), 37% had complete fistula resolution.35 Such comparative data are not available for certolizumab pegol.

Patients who have previously been exposed to anti-TNF therapy appear to have lower absolute response rates to other agents within this class. It is unclear whether previous anti-TNF use is merely a surrogate marker for more serious disease or reflects loss of response to the mechanism of action. The development of antibodies to a specific biologic does not correlate with the development of antibodies to another agent. Among patients previously exposed to anti-TNF therapy, analyses from CHARM, GAIN, PRECiSE-2, ENACT-1 and ENACT-2 show that these biologics can induce and maintain remission among patients previously exposed to infliximab treatment and who lost response or became intolerant.27,28,32,34 The available data, however, do not answer the questions regarding “crossover” therapy for primary nonresponders. In the PRECiSE-2 trial, patients designated as previously exposed to anti-TNF were required to have had a primary response to infliximab but did not necessarily have a secondary loss of response to infliximab.34 Thus, these data do not help answer outstanding questions about crossover therapy or for patients who were primary failures to infliximab. In the ENACT-2 trial, some patients had previously been exposed to infliximab. In this study, previous treatment with infliximab was associated with lower absolute rates of response (54%) and remission (32%) to natalizumab, but natalizumab was superior to placebo response of 15% and remission of 9%.

Mucosal healing, which has been increasingly identified as an important physiologic parameter of treatment success, has been shown among patients receiving infliximab maintenance therapy. No data exist to compare differences between this specific anti-TNF and other biologics. Infliximab has been shown to induce and maintain remission and to facilitate corticosteroid withdrawal in patients with UC.20 The ability of other biologics to treat UC is the subject of intense study; however, insufficient data exist at this time to compare relative efficacy.

**Figure 1.** Design characteristics for biologic trials in CD.

<table>
<thead>
<tr>
<th>Short term induction (Targen/CLASSIC I / ENCORE)</th>
<th>Maintenance (ACCENT / PRECiSE 2)</th>
<th>Induction and maintenance (PRECiSE-I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled induction</td>
<td>Open Label induction</td>
<td>Double-Blind, PLC induction</td>
</tr>
<tr>
<td>Early endpoint (4 weeks, 12 weeks)</td>
<td>Followed by maintenance of response in responders</td>
<td>DB-PLC Maintenance</td>
</tr>
<tr>
<td>Multiple doses of active drug 1:1:1:1 allocation</td>
<td>70-point or 100-point reduction in CDAI</td>
<td>100-point reduction in CDAI</td>
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<tr>
<td>Remission</td>
<td>Remission</td>
<td>Remission</td>
</tr>
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<td></td>
<td>Primary endpoint early and late response combined</td>
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</table>

**What Are the Comparative Toxicities of Biologic Agents in IBD?**

**Assessing adverse drug events.** Given the comparable efficacy of biologics, their relative side effect profiles gain greater importance. However, the absence of head-to-head trials impairs efforts to compare agents within the anti-TNF class and to compare anti-TNFs with natalizumab. The nature and prevalence of short-term and long-term adverse drug reactions associated with biologics continues to unfold, however, reflecting the difficulties inherent in determining adverse drug events (ADEs). Furthermore, significant differences in the sources of available safety data limit detailed comparison.

The recognition of ADEs after clinical introduction of a drug is common. In one study, of more than 500 agents approved by the FDA between 1975 and 1999, more than 10% were removed from the market or withdrawn or acquired a “black box” warning.99 This reflects the difficulties in assigning causalities of side effects to a specific drug and the “learning curve” inherent in new drug use. Causality criteria assess the chronologic relationship between drug use and ADEs, clinical criteria, including preexisting conditions, and imputability, or the intrinsic likelihood that an agent could cause a given reaction.100 The learning curve associated with new drug use reflects its gradual adoption and widened clinical use (Fig-
Only over time do subpopulations of patients become exposed, either intentionally or inadvertently, such as in pregnancy. Use of an agent in combination with other medicines is generally controlled in early studies; thus, medication interactions emerge later. Also, rare ADEs require exposure and observations in large numbers of patients to become apparent. Further complicating our understanding of ADEs is confounding factors attendant to the underlying disease and the nature of various data sources, such as the FDA MedWatch program.

ADE data sources, such as case reports, open series, placebo-controlled randomized clinical trials, postapproval databases, registries supported by pharmaceutical companies and others, and experience from other disease states, vary in their strengths and weaknesses. The strengths of clinical trial data include that patients are prospectively randomized, treatments are standardized, and attempts can be made to control confounding factors and to systematically collect data, allowing better safety comparisons. Such studies are often limited, however, by small patient numbers, the homogeneous natures of subjects, often without comorbidities seen in clinical practice, and limits on how medications are administered (continuous vs intermittent) and whether additional medications are used.

Postmarketing surveillance through spontaneous reporting systems such as MedWatch takes advantage of large patient numbers, enabling detection of uncommon side effects. The inclusion of heterogeneous patient populations with variable comorbidities and concurrent medical treatments more accurately reflects “real world” practice. Data collection from these studies, however, is largely voluntary, creating potential underestimation of ADEs. The true incidence of ADEs cannot be calculated. Registry data are collected more systematically than postmarketing data and may better enable detection of uncommon side effects. These studies also reflect drug effects in heterogeneous patient populations and in conjunction with other medication use. Data from these sources, however, cannot control for unmeasured confounding factors, and patients are not prospectively randomized and treatment is not standardized.

Lastly, confounding factors among patients impact the identification of drug-related complications; patients with IBD have increased risk for infections and some cancers based on many factors, including disease severity, malnutrition, and concomitant use of other medications.

**Nature of side effects associated with biologic therapy in IBD.** Anti-TNF therapies. Due to the nature of their effects on TNF, all anti-TNF therapies share similar ADEs, including increased risk of infections from intracellular pathogens, most notably, TB, other opportunistic infections, autoimmunity, infusion reactions, and other rare, potential side effects such as neurologic disorders, congestive heart failure, and cancer. When considering these side effects, however, it is important to put them in context of other IBD therapies, such as corticosteroids and immune modulators, which also increase the risk of infectious complications.

**TB.** An evaluation of postmarketing surveillance data from the United States among patients with rheumatoid arthritis indicates similar rates of TB with different anti-TNFs: etanercept, 0.01; infliximab, 0.05; adalimumab, 0.02 events per 100 patient-years (data on file, Abbott Laboratories, June 2006).

The reduction of rates of TB among patients treated with anti-TNFs requires careful pretreatment assessment. The manifestations of TB among patients treated with biologic therapy may be unusual and often include extrapulmonary disease. All patients for whom anti-TNF therapy is being considered should undergo a detailed medical history, with attention to previous TB exposure, infection, or disease; previous TB treatment; recent close contact with patients with known or suspected TB; demographic factors (country of origin); social risk factors (homelessness, incarceration, residence in a chronic care facility); occupation; and concomitant medical conditions and treatments, particularly those causing immune suppression. A detailed physical examination should investigate any symptoms of productive, prolonged cough, chest pain, hemoptysis, fever, chills, night sweats, anorexia, weight loss, or easy fatigability. Before starting therapy, a tuberculin skin test (purified protein derivative) and chest radiograph should be performed.

For patients with positive purified protein derivative results and normal findings on chest radiography, treatment of latent TB should be undertaken with guidance from an infectious disease or pulmonary specialist. Treatment is required for those with evidence of active disease, including positive findings on chest radiography and purified protein derivative. Anergy or previous BCG vaccination may obfuscate skin testing results. For patients with a negative purified protein derivative test result, QuantiFERON (Cellestis International, Melbourne, Australia), a more sensitive and specific TB test performed on whole blood samples, should be considered.

**Opportunistic infections.** In addition to TB, a broad range of infections, including opportunistic infections,
have been reported with the use of all TNF inhibitors, with reported serious infection rates for infliximab of approximately 4% in the ACCENT I and II trials,15,17 3.6% with adalimumab when administered every other week in the CHARM trial,27 and 2.8% with certolizumab pegol in the PRECISE 2 trial.32 In a systematic review of pooled data from 9 clinical trials involving 3493 patients with rheumatoid arthritis treated with adalimumab or infliximab, Bongartz et al found a 2-fold increased risk of serious infection.105

The risk of reactivation of granulomatous diseases and infections where host defenses are particularly macrophage dependent is of particular concern and is heightened further by concomitant use of immunosuppressive therapy.106

Malignancies and lymphoproliferative disorders. In a pooled analysis using results of placebo-controlled trials of infliximab and adalimumab in patients with rheumatoid arthritis, the odds ratio for malignancy (including basal and squamous cell cancers) was 3.3 (95% confidence interval, 1.2–9.1).105 This result differs from the Crohn’s Crohn’s Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry data analysis, which did not show a significant increase in rates of cancer between patients treated with infliximab and those patients with IBD who were not.107 Specifically, the relative risk of lymphoproliferative disorders, while elevated at 1.3, was not significant. The difference in these results could be due to the study populations (rheumatoid arthritis vs IBD), the methods (pooled data from placebo-controlled trials vs observational cohort study), or chance. At the time of this conference, 6 cases of hepatosplenic T-cell lymphoma, a rare form of non-Hodgkin’s lymphoma, have been reported in association with infliximab use in young patients with CD (ages 12–31 years), the majority of whom were male.9 Like the majority of the other 120 reported cases of hepatosplenic T-cell lymphoma in the literature, these patients were on concomitant therapy with azathioprine or 6-mercaptopurine. No cases have been reported in UC or in patients with rheumatoid arthritis, the latter who generally do not receive azathioprine. This finding implicates a role for thiopurines but does not exonerate infliximab. Given these data, a link between anti-TNFs and lymphomas or other malignancies cannot be completely excluded yet. It should be noted that the increased risk of cancer observed among patients with rheumatoid arthritis treated with anti-TNF agents in clinical trials occurred in the first year of therapy, suggesting that if such an association is truly causal, it may be through unmasking or accelerating the growth of existing cancers.

Neurologic disorders. Rare reports of optic neuritis, seizure, and new onset or exacerbation of central nervous system demyelinating disorders, including multiple sclerosis, have been reported with the use of anti-TNFs.10 While the majority of these cases have been reported in association with infliximab use, this appears to reflect greater patient exposures. Neurologic complications have emerged with certolizumab pegol and adalimumab use. In patients with preexisting or recent onset of central nervous system demyelinating disorders, the benefits and risks of anti-TNF therapy need considerable scrutiny.

Congestive heart failure. Anti-TNF agents are contraindicated for patients with class III–IV congestive heart failure due to evidence of increased risks of death from several clinical trials.

Autoimmunity. The development of autoantibodies (antinuclear antibodies and anti-DNA antibodies) is common when anti-TNFs are administered. The reported rates of autoimmunity range from <5% at 6 months among certolizumab pegol–treated patients to >50% among infliximab-treated patients.32,104,108 The general clinical relevance of autoantibodies is unclear, rendering such comparative data of limited clinical use. In contrast to the development of antibodies against the anti-TNF, anti-TNF–induced formation of autoantibodies does not reduce the efficacy of TNF therapy and does not cause significant clinical consequences, although occasional lupus-like syndromes have been described. There is no indication for monitoring in patients who have no symptoms.

Infusion and injection site reactions. Infusion reaction rates for infliximab were 17.0% in the ACCENT I trial15 and 7.1%–9.4% in the ACCENT II trial.17 Serious infusion reaction rates were significantly lower (1.0% and 0.3%, respectively). Subcutaneously administered adalimumab and certolizumab pegol can be associated with injection site reactions, although these are generally less serious in nature. More than 4% of patients in the CHARM trial noted injection site irritation and pain during induction. Injection site reactions were reported in 2% of patients during induction.27 This rate increased to as high as 4.8% among those treated with a 40-mg weekly maintenance regimen. Schreiber et al reported that injection site reactions associated with certolizumab pegol reached 6.8% among those treated with 100 mg certolizumab pegol; however, when PRECISE 1 and 2 were considered together, injection site reactions were greater among those given placebo.32

Immune response. Patients frequently develop antibodies against biologic therapies. The significance and management of these antibodies are not well defined. The development of antibodies, while correlated with an increased risk of infusion reactions, is not predictive of infusion reactions in a specific individual. These antibodies can decrease the degree and duration of response, but this correlation is incomplete. High titers of antibodies to infliximab clearly interfere with the pharmacokinetics of the drug. Dose escalation and decreased dosing interval can frequently maintain response. Conversely, attempts to modulate the development of anti-TNF antibodies through concomitant immune suppression do not necessarily prevent the need for dose escalation and/or reduced dosing interval.

In maintenance infliximab studies, rates of antibodies to infliximab ranged from 9% to 17%, and between 31% and 58% had inconclusive antibody results.15,17 In the clinical
trials of adalimumab in CD, 0.7% of patients in CLASSIC I \(^{26}\) and 2.6% in CLASSIC II \(^{109}\) developed antiadalimumab antibodies. Data from the CHARM trial are not available. In the PRECISE 1 and 2 trials, 8% of patients receiving certolizumab pegol 400 mg tested positive for anti-certolizumab pegol antibodies at least once.\(^{31,32}\)

The development of antibodies against infliximab is reduced when concomitant immune suppression is used and when a scheduled maintenance regimen is administered instead of episodic treatment.\(^{29}\) Similarly, data from rheumatoid arthritis trials with adalimumab show higher serum concentrations of adalimumab when administered concomitantly with methotrexate.

**Natalizumab.** Safety data for natalizumab come from more than 3900 patients and 5500 patient-years of exposure. Most common ADEs are comparable to placebo. Compared with other immunomodulators, natalizumab increases the risk of opportunistic infections. The most significant ADE observed to date is the development of PML. Among patients receiving natalizumab for multiple sclerosis or CD, 3 cases of PML have occurred, 2 of which were fatal.\(^{36–38}\) Subsequent analysis of more than 3000 patients exposed to natalizumab but in whom therapy had been discontinued has identified no additional confirmed cases of PML beyond the 3 cases mentioned previously.\(^{39}\) The risk of developing PML is approximately 1 in 1000 patients (95% confidence interval, 0.2–2.8 per 1000) treated with natalizumab for an average of 17.9 months.\(^{39}\)

Biologics afford a significant advance for patients with severe, refractory, or fistulizing IBD. Their ability to improve or resolve disease, particularly in these most severely affected patients, needs to be carefully weighed against their potential risks. Biologics, by their design, attenuate immune response and result in increased risks of infections and potentially increased risks of other serious or fatal side effects. Concomitant therapy with corticosteroids and/or immunomodulators increases the risk of infection. Concomitant therapy with immune suppressants increases the risk of neoplasia.

To attempt to weigh these risks and benefits objectively, Siegel et al modeled a simulation of 2 cohorts of 100,000 patients each, receiving either infliximab or standard therapy.\(^{110}\) Using data based on systematic review of 6 studies reporting ADEs, they made the following assumptions at year 1: 1.6 lymphomas and 4.0 nonlymphoma deaths per 1,000 patients taking infliximab. They calculated that infliximab therapy results in 12,216 more remissions, 4,255 fewer operations, improved quality of life, and 33 fewer deaths from CD. Infliximab, however, resulted in 201 more cases of lymphomas and 249 more all-cause deaths. Using a different approach, Sands et al surveyed patients with CD to assess their willingness to assume risks to potentially benefit from biologic therapy.\(^{111}\) Notably, when faced with moderate to severe disease activity, patients were willing to accept significant risks, even risks for PML and lymphoma. Clearly, the decision to pursue biologic therapy must be individualized and account for both the patient’s disease-related deterioration in quality of life as well as their willingness to assume certain risks. As the true prevalence and nature of ADE become clearer, these calculations will become more explicit.

**What Is the Role of Biologics in the IBD Treatment Paradigm and What Are Important Future Research Considerations?**

Historically, IBD therapy has consisted of “step up” or sequential treatment geared to the severity of the disease. The goal of treatment has been alleviation of symptoms. For some patients, particularly those with corticosteroid-refractory or fistulizing disease, biologics appear more effective in achieving this goal than traditional therapies. Furthermore, data suggest that early use of biologic therapies may slow disease progression and modify disease course.\(^9\) Thus, the appropriate role of biologic therapy in the IBD treatment paradigm, specifically whether it should be used as a first- or second-line therapy, has become the subject of much discussion.

To place biologic therapy in the proper context, a clear understanding of IBD natural history and the relative efficacy and side effects of traditional and biologic therapies is required. Given the heterogeneous nature of IBD and of patient response to biologics, biologics may be unnecessary in some and not beneficial in others. Clinicians need to assess both the complications of drug treatment and those of undertreatment of disease. As previously outlined, biologic therapy has many potential benefits but may also incur increased risk for infections, cancer, significant drug-related side effects, and costs associated with biologic therapies. Undertreatment of disease, however, has risks, including poor quality of life, complications of disease, and the costs associated with active disease and the treatment of complications. The risk and benefit of introducing biologic therapy demands extensive knowledge about both treatment options and patients, including who will need intense therapy (prognosis) and who will respond to such therapy. Many variables in this equation remain unknown and many important outcomes remain undefined or poorly quantifiable, such as reliable evidence of disease modification and reduction in disability.\(^{112}\)

For many patients, existing therapies adequately treat disease. In luminal CD, biologics produce an initial clinical response in about two thirds of patients and remission in about one third of patients. However, only one fourth of responders are in remission at 1 year. Similar induction of remission is seen with corticosteroids and similar maintenance effects with azathioprine and 6-mercaptopurine. Early intervention with azathioprine or 6-mercaptopurine has also led to improved outcomes when administered with the first course of corticosteroids\(^{113}\) or biologics.\(^9\)
In contrast, patients with complex fistulizing anorectal CD have a poor prognosis and respond poorly to traditional therapy. Infliximab and adalimumab are effective in this setting. About 20% of all treated patients maintain the cessation of drainage from fistula over 1 year with an associated reduction in complications and surgeries. No other drugs are of proven benefit in prospective controlled studies.

Have the requisites to use biologic agents as first-line therapies been met at present? In luminal CD, current data do not support the routine use of biologics as first-line therapy. However, some patient subgroups may benefit from early biologic therapy, particularly those with complex fistulizing disease. As data emerge, there may be an early role for those presenting with more extensive disease or early fistulizing disease; however, these data are not yet mature. Currently, data do not exist to administer biologics as first-line therapy in UC.

Better predictors of prognosis and response are needed. Furthermore, better information about both absolute and relative short-term and long-term efficacy, safety, convenience, and costs are needed. Such information would allow clinicians, their patients, and governmental agencies to make much more informed decisions about the use of biologics.

Biologic therapy has rapidly changed the face of IBD treatment and improved the prognosis for many patients unresponsive to previously available therapies. The continued evolution of the role of biologics in IBD is predicated on finding answers to a number of outstanding questions about appropriate markers of prognosis and response, the use of biologics as limited or bridge therapy and its duration, the applicability of biologics early in disease, and potential disease modification. To answer these important questions, more information about the natural history of disease and its complications as well as the complications of biologic therapy is needed. Long-term data about the effects of biologic therapy on hospitalizations, surgeries, and other outcomes must be collected, and the relationship between mucosal healing and these outcomes should be characterized. Specific data regarding immunogenicity and its treatment or prevention and, the development of oral, non–antibody-based therapies, must be explored.

Industry-supported basic and clinical research has yielded significant progress in the field of biologics thus far. For rapid progress to continue, the partnership between pharmaceutical companies and external researchers must continue to evolve. Future trials should have consistent end points, consistent data collection (which includes measurement of therapeutic drug concentrations, CRP levels, and autoimmunity), comprehensive data collected from pediatric and pregnant patients, and routine collection of serum DNA and RNA. Furthermore, such comprehensive data should be publicly available to foster complete data analysis, which we anticipate will serve to accelerate the rate at which our understanding and appropriate use of biologic therapy grow.

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Participants in the conference have indicated they have the following financial relationships with companies that market drugs and devices to gastroenterologists:

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