Biological Therapies for Inflammatory Bowel Diseases

PAUL RUTGEERTS, SEVERINE VERMEIRE, and GERT VAN ASSCHE
Division of Gastroenterology, University of Leuven Hospitals, Leuven, Belgium

Crohn’s disease and ulcerative colitis are chronic disabling inflammatory bowel diseases (IBDs). Although the causes of IBD are unknown, defects in innate and adaptive immune pathways have been identified and biological therapies that target key molecules have been designed. Infliximab, a chimeric immunoglobulin (Ig)G1 monoclonal antibody to tumor necrosis factor, dramatically improved treatment of patients with Crohn’s disease and ulcerative colitis. Infliximab has achieved treatment goals such as mucosal healing and decreasing the need for hospitalizations and surgeries. Although several anti–tumor necrosis factor therapies have been developed, there is a great need for drugs that target other pathways. Natalizumab, an antibody against the integrin α4β7 subunit, blocks leukocyte adhesion and has reached the clinic in the United States but has not been approved in the European Union; other anti-adhesion molecules currently are under development. Additional approaches under clinical development include therapeutics that target cytokines, such as interleukin-12/23, as well as those that block T-cell signaling. The use of recombinant human proteins, including immunoregulatory cytokines and growth factors, has not been successful so far. The efficacy of each therapy must be shown in carefully designed clinical programs. Biological therapies carry a definite safety risk, so their place in treatment algorithms must be defined carefully.

Inflammatory bowel diseases (IBDs) are a group of chronic systemic diseases involving inflammation of the gastrointestinal tract. IBDs include ulcerative colitis, which affects only the large bowel; Crohn’s disease, which can affect the entire gastrointestinal tract; and indeterminate colitis, which consists of large-bowel inflammation that shows features of both Crohn’s disease, ulcerative colitis, and microscopic colitis. The pathogenesis of IBDs is not well understood. No single infectious microorganism has been identified that causes these diseases, and the genetic factors that permit predisposition to IBDs are being unraveled. The current premise is that defects in the innate immune system allow bacteria to invade the mucosa of the gut, resulting in an exaggerated adaptive immune response, which leads to extensive bowel damage. It is not clear why in ulcerative colitis the inflammation is confined to the mucosal layer of the colon and spread diffusely, whereas in Crohn’s disease the inflammation is transmural and has a segmental distribution that can affect the entire gastrointestinal tract.

The ideal therapeutic strategies for patients with Crohn’s disease and ulcerative colitis would induce remission and maintain long-term remission without steroid exposure and with minimal surgeries. Corticosteroids have been used in the treatment of active IBD for many decades and are effective in inducing clinical remission of Crohn’s disease and ulcerative colitis. However, corticosteroids are not effective for maintenance of remission and their long-term use is associated with sometimes severe and irreversible side effects. Topically acting steroids have fewer side effects than systemic steroids but also are not effective in maintaining remission. Within 1 year from the start of steroid therapy, most patients relapse or develop corticosteroid dependency. Other patients are refractory or become refractory to corticosteroids, not responding to even high doses. The thiopurine immunosuppressive agents azathioprine and 6-mercaptopurine are effective steroid-sparing drugs that maintain remission in patients with Crohn’s disease. Their full...
effect is not reached until 12–16 weeks after initiation of dosing, although steady-state 6-TG thioguanine levels are observed by 2 weeks. The efficacy of azathioprine in ulcerative colitis is less well established. Ardizzone et al showed that azathioprine is more effective than mesalamine in inducing steroid-free clinical and endoscopic remission at 6 months (53% vs 19%; \( P = .006 \); odds ratio, 4.78) in patients with steroid-dependent ulcerative colitis. Methotrexate is effective in inducing and maintaining remission in patients with Crohn’s disease, but its use in patients with ulcerative colitis has not been investigated thoroughly.

In patients with severe ulcerative colitis, intravenous doses of cyclosporine A (4 mg/kg) are an effective rescue therapy that allows patients to avoid surgery (a dose of 2 mg/kg is equivalent in efficacy to 4 mg/kg and carries a lower incidence of overall side effects). This strategy is only valuable in patients in whom remission can be maintained with azathioprine. However, even with this strategy the majority of patients eventually need colectomies. The introduction of biologics such as infliximab has changed the treatment of refractory IBD dramatically; many of these are either approved or are likely to enter the market. What pivotal studies have shown the efficacy of these agents? Biological therapies help to correct the imbalance of the gut immune system causing the diseases. Although the cause of IBD is unknown, many molecules that are involved in the disease process have been identified and can be targets of biological therapies. We first will review the biological agents that have proven successful and are routinely used in the clinic, then discuss promising agents for which definitive proof of efficacy has not been established, and, finally, discuss biological approaches that have failed.

**Biologic Therapies With Proven Efficacy**

**Anti–Tumor Necrosis Factor Strategies**

Tumor necrosis factor (TNF) (also known as TNF-α) is a proinflammatory cytokine that induces cell proliferation and differentiation; its signaling pathways regulate gene expression and up-regulate adhesion molecules. TNF promotes the inflammatory response in various diseases including rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease and ulcerative colitis, and psoriasis. Symptoms of these disorders improve upon therapy with TNF inhibitors. Three anti-TNF molecules are used currently to treat IBD: infliximab, adalimumab, and certolizumab pegol. Etanercept, which links human soluble TNF receptor 2 to the Fc component of human immunoglobulin (Ig)G1 and oncept, a recombinant, soluble human p55 receptor to TNF-α have not been shown to be effective in treating Crohn’s disease.

Infliximab is a chimeric monoclonal IgG1 against TNF that has proven to be a highly efficacious induction and maintenance agent in patients with refractory luminal and fistulizing Crohn’s disease. The ACCENT I studies have shown that scheduled maintenance therapy with infliximab is superior to episodic therapy to maintain response and remission both in luminal and in fistulizing Crohn’s disease. Infliximab also induces rapid and profound endoscopic healing, improves quality of life, and allows patients to avoid hospitalization and surgery. Therapy with infliximab also has proven highly effective in children with refractory Crohn’s disease. The optimal treatment schedule is the same as in adults and successful therapy with this anti-TNF agent induces weight gain, restores growth, and improves bone formation in children.

Infliximab is administered as an intravenous infusion at a dose of 5 mg/kg body weight at weeks 0, 2, and 6, followed by 5-mg/kg infusions every 8 weeks for maintenance. The combination of infliximab and azathioprine is more effective than infliximab alone to induce steroid-free remission and mucosal healing of the bowel in luminal Crohn’s disease when given for up to 24 weeks to patients who were not treated previously with azathioprine. The Study of Biologic and Immunomodulator Naive Patients in Crohn’s Disease (SONIC) also showed that infliximab monotherapy is significantly better for inducing steroid-free remission and mucosal healing than azathioprine alone in azathioprine-naive patients.

In contrast, there seems to be no synergism between methotrexate and infliximab for the induction and maintenance of steroid-free remission in luminal Crohn’s disease. It is less clear whether it is beneficial to use the infliximab-azathioprine combination in patients who previously failed therapy with azathioprine. In that setting the combination of infliximab and azathioprine has not been observed to be more effective than only infliximab when given beyond 6 months and because of the increased safety risk of combination therapy we recommend that azathioprine therapy be discontinued after 6 months of combination treatment. A large, open cohort study of patients with Crohn’s disease who were given infliximab for many years showed a sustained benefit if the dose was adjusted when the treatment effects decreased. Surprisingly, infliximab also has proven to be effective in the treatment of refractory ulcerative colitis and for rescue from cortisone-resistant presurgical ulcerative colitis. The Active Ulcerative Colitis (ACT) trials showed that induction with intravenous infliximab 5 mg/kg at weeks 0, 2, and 6 followed by scheduled maintenance therapy every 8 weeks is effective in refractory moderate-to-severe ulcerative colitis to improve the disease, to induce remission, to heal the mucosa, and to decrease the need for steroids over 54 weeks. In patients with acute severe ulcerative colitis resistant to high doses of glucocorticosteroids a single infusion of infliximab 5 mg/kg reduced the need for colectomy at 3 months from 67% with placebo to 29% (\( P = .017 \)).
The indications for infliximab therapy are summarized in Table 1. The main problem with infliximab is that it is an important proportion of patients develop antibodies to infliximab, formerly called human antichimeric antibodies, because of the presence of foreign sequences in the variable, complementarity-determining regions of the antibody. These antibodies to infliximab predispose to acute infusion reactions and delayed serum sickness-like reactions and secondary loss of response.29–31 Several treatment strategies, including scheduled maintenance therapy, concomitant immunosuppression, and prophylactic systemic steroids, have been proposed to decrease the incidence and the impact of antibodies to infliximab. Nevertheless, at least 10% of patients each year have to stop therapy because of intolerance and/or loss of response, even on scheduled maintenance therapy.26,32

Hence, there was and there still is an important need to develop other anti-TNF agents including other monoclonal antibodies to TNF. In parallel with infliximab, 2 more humanized anti-TNF agents were developed (Figure 1 and Table 2). Adalimumab (Humira; Abbott) is a fully human recombinant human IgG1 monoclonal antibody against TNF approved for use in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and to treat luminal Crohn’s disease. Unlike infliximab, adalimumab is administered by subcutaneous injection and easily can be self-administered every 2 weeks. The pivotal trials are the Clinical Assessment of Adalimumab Safety and Efficacy Studied as an Induction Therapy in Crohn’s disease I (CLASSIC I) and CLASSIC II, Crohn’s trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM), and Gauging Adalimumab Effectiveness in Infliximab Nonresponders (GAIN) studies. The CLASSIC-I was a dose-finding induction study33 with remission at week 4 as the primary end point (Crohn’s disease activity index [CDAI] score, <150). There was a clear dose-response effect. Remission was achieved in 18%, 24%, and 36% of patients in the adalimumab 40/20 mg, 80/40 mg, and 160/80 mg groups, respectively, compared with 12% in the group that was given placebo (P = .001 for the 160/80 mg group vs placebo). The efficacy of maintenance therapy with adalimumab 40 mg subcutaneously (sc) every 2 weeks through 56 weeks was shown in the CLASSIC II trial.34

In the phase III Crohn’s trial of the Fully Human Antibody Adalimumab for Remission Maintenance,35 patients with moderate to severely active Crohn’s disease received open-label induction therapy with subcutaneous adalimumab (80 mg) at weeks 0 and 40 mg at week 2 and then were assigned randomly to groups that were given adalimumab 40 mg every week, 40 mg every 2 weeks, or placebo. Fifty-eight percent of the patients displayed a clinical response. Both dosing regimens of adalimumab maintenance therapy were associated with significantly greater clinical remission rates (CDAI, <150) at week 26 (47% and 40%, respectively) and week 56 (41% and 36%, respectively) compared with placebo (17% and 12%, respectively; P < .001). At week 56, 23% of patients receiving weekly adalimumab and 29% of patients receiving adalimumab every 2 weeks were able to discontinue steroids while maintaining remission, compared with 6% in the placebo group (P ≤ .001).

A key question is whether adalimumab is able to rescue patients who lost response or are intolerant to other anti-TNFs (such as infliximab). The study Gauging Adalimumab Effectiveness in Infliximab Nonresponders36 was a randomized, double-blind, placebo-controlled analysis of 325 patients with moderate to severe Crohn’s disease who had lost previous response or were intolerant to infliximab. At week 4, 21% of the patients who had received adalimumab 160 mg at week 0, followed by adalimumab 80 mg at week 2 achieved remission, compared with 7% on placebo (P < .001). The rates of response and remission in the Gauging Adalimumab Effectiveness in Infliximab Nonresponders study (patients who already had been exposed to infliximab) clearly were lower than the rates observed in the CLASSIC trial and the Crohn’s trial of the Fully Human Antibody Adalimumab for Remission Maintenance, in patients who had not previously received anti-TNF therapies. Hence, it seems that a proportion of patients is developing genuine resistance to anti-TNF strategies overall and not only to a single agent. Controlled studies of the use of infliximab or certolizumab pegol in patients who have lost response to or have become intolerant to adalimumab have not yet been performed.

Certolizumab pegol or CDP-870 (Cimzia; Celltech/UCB, Slough, UK) is a pegylated humanized fragment antigen binding (Fab) that binds TNF; it is administered sc and has been approved in the United States for treatment of Crohn’s disease. After 2 phase II clinical studies
produced equivocal results, 2 large placebo-controlled phase III studies were performed. Pegylated Antibody Fragment Evaluation in Crohn’s Disease: Safety and Efficacy (PRECISE)-1 and PRECISE-2 were designed to evaluate the efficacy of certolizumab pegol in inducing and maintaining a response in patients with Crohn’s disease. In the PRECISE-1 study, 662 patients with moderately to severely active luminal Crohn’s disease (CDAI, 220–450) were assigned randomly to groups that were given certolizumab pegol 400 mg or placebo at weeks 0, 2, and 4, and then every 4 weeks through week 24. The primary end points were clinical response (decrease in CDAI, ≥100) at weeks 6 and 26 in patients with baseline C-reactive protein (CRP) levels of 10 mg/L or higher. At week 6, 26% of the placebo and 37% of the certolizumab pegol–treated patients had a clinical response (P < .05); at weeks 6 and 26, the rates were 12% and 22%, respectively (P = .05). In the PRECISE-2 study, 668 adult...
patients with Crohn’s disease (CDAI, 220–450) received open-label induction therapy with certolizumab pegol, 400 mg, at weeks 0, 2, and 4. At week 6, the 428 of 668 patients with Crohn’s disease (64%) who responded to therapy were assigned randomly to groups that were given maintenance therapy with certolizumab pegol 400 mg (n = 216) or placebo (n = 212) every 4 weeks through week 24. The primary end point was maintenance of clinical response at week 26 in a subgroup of patients with baseline CRP levels of 10 mg/L or higher (112 certolizumab pegol patients and 101 placebo patients). The clinical response rates at week 26 were 61.6% and 33.7% for certolizumab pegol and placebo, respectively (P < .001) in the CRP of 10 mg/L or greater group. In the overall intent-to-treat analysis, at week 26 the clinical response rates were 62.8% and 36.2% for certolizumab pegol and placebo, respectively (P < .001) A post hoc analysis of 278 (42%) patients with remission at week 6 showed that significantly more patients maintained remission throughout week 26 in the group given certolizumab pegol compared with placebo (61% vs 34%; P < .001).

Although there are no comparative trials available for the 3 different anti-TNF agents, it seems that infliximab, adalimumab, and certolizumab pegol have comparable efficacy, especially for maintenance of remission. In patients naive to anti-TNF therapy, higher doses of these agents has not been shown to be more effective than the standard doses and only if there is loss of response may higher doses be needed to maintain response. Immunogenicity is more of a problem with infliximab than with the other drugs, but none should be administered on an episodic basis because of the risk of formation of anti-therapeutic antibodies. Although the combination of infliximab with azathioprine is superior to infliximab alone for achieving steroid-free remission over the course of 24 weeks in patients with active luminal Crohn’s disease, there is no current evidence to suggest that combining adalimumab or certolizumab pegol with azathioprine is beneficial, although this has not been studied formally. A key feature determining efficacy of any anti-TNF drug are the trough levels achieved. Response loss to each of the agents is mostly the consequence of increased clearance of the drug and dose escalation restores the effect in most patients. Dose escalation with infliximab usually involves a decrease of the interval between infusions but sometimes dose increase to 10 mg/kg is necessary to restore the drug effect. The ACCENT I study18 showed that up to 90% of patients with luminal Crohn’s disease who lose response to infliximab can be rescued by dose escalation, and the ACCENT II17 study showed that in fistulizing disease rescue by dose escalation was successful in up to 60% of the patients.

On loss of response to adalimumab dose escalation is performed by administering adalimumab 40 mg sc weekly instead of every 2 weeks. Dose escalation with certolizumab pegol usually is performed by giving 400 mg sc every 2 weeks instead of every 4 weeks. Patients who have lost response to one anti-TNF agent even after dose adjustment usually can be treated successfully with a second anti-TNF monoclonal antibody. There is, however, a decrease in the proportion of patients who will respond to the second-line anti-TNF, suggesting resistance develops in some patients, not only to anti-TNFs but also to other biological therapies, such as natalizumab (see later). The anti-TNFs have similar safety profiles and the risk of opportunistic infections, such as tuberculosis, as well as demyelination and complications in patients with congestive heart failure are a class-specific problem for these reagents. There are now case-control cohorts revealing that the rate of severe complications with infliximab is not higher than that in patients with IBD treated with other medications.39,40

The choice for the first anti-TNF agent will depend greatly on personal preference by the treating physician and the patient’s perspectives on convenience issues. Sequential use of different anti-TNF agents in patients who have responded well to a first agent is preferred over an immediate switch to natalizumab. It must be emphasized that for most indications, including fistulizing Crohn’s disease and ulcerative colitis, the evidence for efficacy presented in clinical trials has been more robust for infliximab than for the other anti-TNFs. Early introduction of anti-TNF therapy also currently is being investigated. Altering the course of Crohn’s disease in the long term requires early complete suppression of inflammation. In patients with early Crohn’s disease the combination of infliximab with azathioprine is significantly better at inducing remission at 1 year and mucosal healing at 2 years than sequential step-up therapy.41

More studies are necessary to show whether the anti-TNFs are able to decrease bowel damage in Crohn’s disease whereas decreasing joint damage with these agents has been shown clearly in rheumatoid arthritis.

**Selective Anti-Adhesion Molecules**

Agents that block interactions between adhesion molecules on circulating immune cells and their endothelial cell receptors would be expected to decrease the migration of these cells through the endothelium, thereby decreasing chronic inflammation. Natalizumab (Tysabri, formerly known as Antegren, Elan Pharmaceuticals [Elan; San Francisco, CA] and Biogen Idec [Biogen; Cambridge, MA]) is a recombinant humanized IgG4 monoclonal antibody to α4 integrin that blocks adhesion and subsequent leukocyte migration into the gut. It is a member of the new class of molecules known as selective adhesion molecule inhibitors (Figure 2A). After 1 week of natalizumab administration, the total number of circulating leukocytes (including lymphocytes, monocytes, basophils, and eosinophils) increased owing to inhibition of transmigration out of the vascular space. This therapy did not affect the number of circulating
Figure 2. (A) Leukocyte adhesion in high endothelial venules of the gut is a multistep process. Fast-moving immune cells are first slowed down by interaction of selectins and nonactivated integrins with their respective ligands expressed by endothelial cells. This causes tethering and rolling of leukocytes close to the endothelial surface. Chemokines secreted from sites of inflammation diffuse through the endothelial layer, bind to chemokine receptors, and activate integrins. Integrin activation is inhibited by CCX-282B, an oral CCR9 inhibitor. Firm adhesion is the last step before leukocyte diapedesis through endothelial pores and results from strong binding between activated $\alpha_4\beta_7$-integrins with their ligand, mucosal addressin cellular adhesion molecule-1 (MadCAM-1). (B) Because MadCAM-1 is expressed specifically in gut lymphoid tissue and interacts with $\alpha_4\beta_7$ integrins but not with other integrins, this crucial interaction can be targeted selectively by the anti-MadCAM-1 mAb PF00547659 and by anti-$\beta_7$-integrin mAbs such as MLN-0002 and rhuMab-$\beta_7$. Endothelial cells in other organs such as the brain, bone marrow, and kidney express $\alpha_4\beta_1$ integrins, which interact with their respective ligand, vascular cell adhesion molecule-1 (VCAM-1). The anti-$\alpha_4$-integrin mAb natalizumab blocks both $\alpha_4\beta_1$-integrin/VCAM-1 and $\alpha_4\beta_7$-integrin/MadCAM-1 interactions. Therefore, it does not selectively inhibit leukocyte trafficking to the gut.
neutrophils. Serum vascular cellular adhesion molecule-1 levels also were reduced significantly in natalizumab-treated patients.

The phase III studies Evaluation of Natalizumab As Continuous Therapy (ENACT) consisted of 2 controlled trials, ENACT-1 and ENACT-2. In ENACT-1, 905 patients with moderately to severely active Crohn's disease were randomized 4:1 to receive 300 mg of natalizumab (n = 724) or placebo (n = 181) at weeks 0, 4, and 8. At 10 weeks, the natalizumab and placebo groups had similar rates of response (56% and 49%, respectively), and remission (37% and 30%, respectively; P = .12). However, post hoc analysis showed significantly greater response and remission rates for natalizumab than for placebo in patients with increased CRP levels (n = 660), active disease despite concurrent immunosuppressant use (n = 300) or prior anti-TNF therapy. ENACT-2 evaluated the efficacy of natalizumab as maintenance therapy. A total of 339 responders to natalizumab in the ENACT-1 trial were randomized to receive 300 mg natalizumab or placebo (1:1) every 4 weeks from weeks 12 through 56, and were followed up until week 60. A sustained response to natalizumab of those who responded previously in the ENACT-1 trial through week 36 was the primary efficacy end point of ENACT-2. Sixty-one percent of natalizumab-treated patients had a sustained response through week 36, compared with 28% in the placebo group (P < .001). The remission rate at week 36 was 44% in the natalizumab-treated group compared with 26% in the placebo group (P = .003). The rates of both sustained clinical response and remission were significantly better in the natalizumab-treated group compared with the placebo group at every time point, starting at week 20. Natalizumab also had clear steroid-sparing capacity.

The efficacy of natalizumab as an induction agent was evaluated in another phase III induction study. Efficacy of Natalizumab in Crohn's Diseases Response and Remission (ENCORE). This study was an international, double-blind, placebo-controlled trial involving 114 sites. In this study, 510 patients with moderate to severely active Crohn's disease and evidence of active systemic inflammation (CRP, >2.87 mg/L) were assigned randomly to groups that were given natalizumab (300 mg) or placebo at weeks 0, 4, and 8. Fifty-one percent of patients receiving natalizumab responded to the initial infusion whereas 37% in the placebo group showed a response (P = .001). At week 8, the difference still was significant, with 48% of natalizumab-treated patients with a clinical response, compared with 32% of the placebo group (P < .001). Furthermore, significantly more patients in the treatment group achieved clinical remission at weeks 8 and 12 (26% vs 16%, respectively; P = .002). The response and remission rates as well as steroid-free remission for natalizumab were superior to placebo at all time points beginning at week 4.

The combined safety data for natalizumab in clinical studies suggests that the drug generally was well tolerated. Antibodies to natalizumab were detected in 8% and 9% of natalizumab-exposed patients in ENACT-1 and ENACT-2, respectively. Concomitant immunosuppressive and corticosteroid therapy appeared to be moderately protective against antibody formation in both trials. Natalizumab was withdrawn voluntarily from the market in February 2005 for safety evaluation after 1 fatal and 1 nonfatal case of progressive multifocal leukoencephalopathy (PML) occurred in the group of 1869 patients who were given natalizumab, in combination with interferon (IFN)-β1a (Avonex), over a 2-year period for treatment of multiple sclerosis. A second death from PML was attributed to natalizumab and involved a patient with Crohn's disease; this patient received 8 doses of natalizumab over an 18-month period and had received multiple immunosuppressant agents and suffered from chronic lymphopenia. Although the 3 cases of PML are very concerning, a detailed review by Yousry et al of the more than 3000 patients who had received natalizumab for multiple sclerosis, Crohn's disease, or rheumatoid arthritis, found no new cases of PML and suggested a risk of PML of about 1 per 1000 patients treated with natalizumab for a mean duration of 17.9 months. Natalizumab was reintroduced to the market for multiple sclerosis and also has been approved in the United States for treatment of Crohn's disease. Because of the risk of PML, natalizumab is available only through a special restricted distribution program called the MS-TOUCH Prescribing Program. A similar program (CD-TOUCH) is available for patients with Crohn's disease (www.elan.com). The drug is not approved for Crohn's disease in Europe.

Recently, 4 new cases of PML have been reported in patients treated with natalizumab as a monotherapy for multiple sclerosis in Europe. This opportunistic infection has been found to be associated with treatment with other biological therapies including monoclonal antibodies to CD20 (rituximab) and CD11a (efalizumab). The exact place of anti-α4-integrin strategies in the therapy of Crohn's disease is not clear yet. A screening strategy for patients at risk for PML needs to be developed if anti-α4 therapies are to be used widely. It is more probable that antimigration strategies that are gut specific will be preferred in the future, if equal efficacy and better safety can be shown (Figure 2B).

The humanized anti-αβ4-integrin antibody MLN-0002 (vedolizumab; formerly MLN-02 and LDP-02) inhibits only gut-specific Madcam-1–mediated leukocyte adhesion (Figure 2). Therefore, this compound is being developed only for ulcerative colitis and Crohn's disease, and not for multiple sclerosis (in contrast to natalizumab). The half-life of this antibody is comparable with that of natalizumab and doses from 0.15 to 2.0 mg/kg have been used in clinical trials. A multicenter, double-blind, placebo-controlled trial was performed involving 181 patients with active ulcerative colitis who were given 2 intravenous doses, 28 days apart, of 0.5 mg/kg or 2.0 mg/kg MLN-0002 (or an identical-
appearing placebo). At week 6, clinical remission rates were 33%, 32%, and 14% in the groups given 0.5 mg/kg MLN-0002, 2.0 mg/kg MLN-0002, or placebo, respectively (P = .03); percentages of patients who improved by at least 3 points on the ulcerative colitis clinical score were 66%, 53%, and 33%, respectively (P = .002). Remission was observed by endoscopy in 28% of patients given 0.5 mg/kg MLN-0002 and 12% given 2.0 mg/kg MLN-0002, compared with 8% given placebo (P = .007). For the minority of patients in whom an MLN-0002 antibody titer greater than 1:125 developed, incomplete saturation of integrin α4β7 was observed on circulating lymphocytes and no benefit of treatment was identified. The MLN-0002 antibody was shown effective also in Crohn’s disease. Although the primary end point of response was not met in the trial therapy with the higher dose of 2.0 mg/kg MLN-0002, antibody was significantly more effective than placebo to induce remission by 2 months. Formation of antibodies to this humanized antibody is associated with lower clinical efficacy.47

Monoclonal antibodies to Madcam-1 and the integrin β4 subunit currently are being tested in clinical trials. It is likely that there will be a place for gut-specific selective adhesion molecule inhibitors in the treatment of Crohn’s disease and ulcerative colitis, certainly as an option for patients who did not respond to anti-TNF agents. If effective and safe, these gut-specific therapies will be tested as primary options and would expand our therapeutic possibilities.

Promising New Biologic Therapies

Anti–Interleukin-12/Interleukin-23 p40 and Anti–IFN-γ Antibodies

Interleukin (IL)-12 and IL-23 have been implicated in the pathogenesis of Crohn’s disease. Naive CD4+ T cells differentiate into several functional lineages characterized mainly by their dependent cytokines. CD4+ T-cell phenotypes include T-helper 1 (Th1), Th2, Th17, and CD4+ T-regulatory cells. Their differentiation and survival depends on the relative abundance of key regulatory cytokines produced mainly by macrophages and dendritic cells. In the presence of IL-12, a heterodimer of p40 and p35 subunits, naive CD4+ T cells adopt a Th1 phenotype and produce IFN-γ to mediate cellular immunity. IL-12 and IFN-γ act in a positive feedback loop. In the presence of IL-6, transforming growth factor-β, and IL-23, a heterodimer of the same p40 subunit as IL-12 and a unique p19 subunit, naive human CD4+ T cells adopt a Th17 cell profile, characterized by the production of IL-17A, IL-17F, IL-22, and IL-21 to mediate cellular immunity. The relative role of the IL-12/IFN-γ and the IL-23/IL-17 axis in human Crohn’s disease has not been elucidated fully, but both pathways have been targeted by selective biological agents.

The IL-12/IL-23 p40 subunit is targeted by the human IgG1 monoclonal antibodies ABT-874 (Abbott, Abbott Park, IL) and CNTO-1275 ustekinumab (Centocor, Malvern, PA) (Figure 3). A phase II study of subcutaneous ABT-874 at doses of 1 mg/kg and 3 mg/kg or placebo weekly with either a 4-week interval between the first and second injection or no interruption for 7 weeks in 79 patients with active Crohn’s disease showed efficacy for induction of response (75% vs 25%; P = .03) and a trend for remission (38% vs 0%; P = .07) in the group given continuous 3-mg doses.48 Decreases in the secretion of IL-12, IFN-γ, and TNF by colonic lamina propria mononuclear cells were observed in patients who responded to anti–IL-12 treatment. A higher proportion of patients given ABT-874 experienced injection site reactions, compared with controls, and 3 of 79 patients developed antidrug antibodies that interfered with drug levels in 2 patients.

The safety and efficacy of either a single intravenous infusion or 4 sc injections of ustekinumab were evaluated in a 54-week phase II study in patients with moderate to severe Crohn’s disease.49 The complicated study design precluded clear conclusions about efficacy. Intravenous administration was not clearly superior to subcutaneous injection. The treatment effects were greatest in patients who already had been treated with infliximab, making ustekinumab a potential therapeutic alternative for this patient population. The relative importance of blocking IL-12 or IL-23, both targeted by ABT-874 and CNTO-1275, for the efficacy of these biologics is at present not at all clear. There are no data for the use of anti–IL-12/IL-23 in ulcerative colitis. Monoclonal antibodies to IL-17 have been developed and trials in Crohn’s disease are underway.

IFN-γ is secreted by Th1 cells. It promotes antigen presentation by macrophages, suppresses Th2 cell activity, causes epithelial cells to express class II major histocompatibility complex molecules, promotes adhesion and binding required for leukocyte migration, and promotes natural killer cell activity.

Fontolizumab (Huzaf; Protein Design Labs, Fremont, CA) is a humanized IgG1 monoclonal antibody against IFN-γ. In a dose-finding study,50 45 patients with a CDAI of 250–450 were enrolled in a double-blind, placebo-controlled, dose-escalation study and assigned randomly to groups that were given single doses of fontolizumab (0.1, 1.0, and 4.0 mg/kg) or placebo. By day 29, patients with clinical response were re-randomized to receive 3 additional doses of half their initial fontolizumab dose or placebo at 4 weekly intervals. No differences in clinical activity were noted between groups given fontolizumab and placebo; the patients given placebo had a high response rate (60% response and 40% remission). By day 29, there were greater decreases in median Crohn’s disease endoscopic index of severity scores (P = 0.02) and serum CRP levels (P < .001) in the group given 4.0 mg/kg (n = 14) fontolizumab compared with the group given placebo (n = 10). In a second phase II study51 133 patients with CDAI scores ranging from 250 to 450 were assigned randomly to groups that were given placebo or fontolizumab (4 or 10 mg/kg). Forty-two patients received 1
dose and 91 patients received 2 doses on days 0 and 28. There was no statistically significant difference in the primary end point of the study (clinical response) between the fontolizumab and placebo groups after a single dose at day 28. However, at day 56, higher response rates were observed in patients given fontolizumab compared with placebo: 69% (22 of 32, \( P < 0.005 \)) for the 4-mg/kg dose; 67% (21 of 31; \( P < 0.03 \)) for the 10-mg/kg dose; and 32% (9 of 28) vs for the placebo group. Stratification according to increased baseline CRP levels resulted in a decreased placebo response and more pronounced differences in clinical benefit. However, the fontolizumab clinical development program has not been continued.

Reagents that inhibit IL-12/IL-23 and IFN-\( \gamma \) should be investigated further as therapeutics for IBD. Based on mucosal cytokine profiles of patients with active IBD reagents that target IL-12 would be expected to be effective against Crohn’s disease but not ulcerative colitis. Drugs that block IFN-\( \gamma \) should be explored further for treatment of both diseases.

**Anti–IL-6–Receptor Antibodies**

IL-6 acts as both a proinflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response leading to inflammation. IL-6 is one of the most potent mediators of...
the acute-phase response. There is not much clinical data available on blockade of this pathway in the treatment of IBD. Tocilizumab is a humanized monoclonal antibody that blocks both membrane-bound and soluble IL-6 receptor. In animal models of colitis this resulted in decreased production of proinflammatory cytokines by the colonic mucosa and induced apoptosis of lamina propria T-cells.

In a pilot placebo-controlled study\textsuperscript{52} investigating the efficacy, pharmacokinetics, and safety of tocilizumab, 36 patients with active Crohn’s disease (CDAI, ≥150) were assigned randomly to receive biweekly intravenous infusion of placebo or tocilizumab, or alternated between tocilizumab and placebo, for 12 weeks at a dose of 8 mg/kg. At the final evaluation, 80% of the patients (8 of 10) given biweekly tocilizumab had a clinical response compared with 31% of the patients who were given placebo (4 of 13; \(P = 0.019\)). Two of 10 (20%) patients on this regimen went into remission (CDAI, <150), compared with none of the placebo-treated patients (0 of 13). The clinical response rate of the every-4-week regimen was 42% (5 of 12). The serum concentrations of tocilizumab were detected at 2 weeks after every infusion, at which time acute-phase responses were suppressed completely; however, they were not suppressed at 4 weeks. There is a need for a large placebo-controlled trial evaluating this therapy in patients with Crohn’s disease and ulcerative colitis. It is not clear whether the development of tocilizumab will be continued for patients with IBD.

**Biological Therapies Without Established Efficacy**

**Recombinant Human Cytokines**

Systemic administration of both recombinant human IL-10 and recombinant human IL-11 have been investigated as treatments for Crohn’s disease and ulcerative colitis but both programs have been discontinued because of a lack of efficacy in controlled trials. Animal studies showed that local administration of IL-10 to the colon via genetically engineered *Lactococcus lactis* bacteria that are administered orally allows for the achievement of high colonic mucosal concentrations of IL-10, resulting potentially in increased efficacy.\textsuperscript{53} A phase I study in Crohn’s disease yielded promising results\textsuperscript{54} and this therapy is now being investigated in ulcerative colitis.

IFNs \(\alpha\) and \(\beta\) are produced by virally infected cells and inhibit viral replication within host cells, activate natural killer cells and macrophages, and increase antigen presentation to lymphocytes. IFNs \(\alpha\) and \(\beta\) have been investigated in Crohn’s disease and ulcerative colitis without success. Two doses of IFN-\(\beta\)-1a, 44 or 66 mcg, or placebo, sc 3 times weekly for 8 weeks have been evaluated in patients with moderately active ulcerative colitis. Endoscopically confirmed remission at 12 weeks was not better for IFN-\(\beta\)-1a than for placebo.\textsuperscript{55}

**Blockade of T-Cell Activation**

Complete T-cell activation requires 2 signals. The first signal is mediated by the interaction of the T-cell receptor complex, which includes CD4 and CD3, with the antigenic peptides presented by major histocompatibility complex molecules on the surface of antigen-presenting cells. The second signal, the co-stimulatory signal, is antigen nonspecific and is provided by the interaction between co-stimulatory molecules expressed on the membrane of antigen-presenting cells and the T-cell. Activation of T cells without co-stimulation leads to T-cell anergy, T-cell deletion, or the development of immune tolerance.

Reagents that blocked CD4 were under development for treatment of Crohn’s disease, but were found to cause long-term depletion of lymphocytes in some patients\textsuperscript{56} (Figure 4). Visilizumab (HuM291, Nuvion; Protein Design Labs) is a non-fragment crystalizable region (FcR)-binding anti-CD3 monoclonal antibody directed against the invariant CD3\(\varepsilon\) chain of the T-cell receptor. This compound was studied in patients with severe refractory ulcerative colitis and fistulizing Crohn’s disease.

An open-label, phase I/II trial in patients with severe steroid-refractory ulcerative colitis was initiated in several US academic centers and preliminary results were promising. Eight patients received a 15-\(\mu\)g/kg intravenous bolus dose of visilizumab on 2 consecutive days and 2 others received 10 \(\mu\)g/kg. Remission was achieved after 1 month in 7 of the 8 patients in the 15-\(\mu\)g/kg group and after 15 days in 2 of the 2 patients in the 10-\(\mu\)g/kg group (Modified Truelove and Witts Severity Index, <4). A clinical response was observed in 8 of the 8 patients in the 15-\(\mu\)g/kg group (Modified Truelove and Witts Severity Index, <10). All 8 patients in the high-dose group showed improvement based on endoscopic evaluations; endoscopic lesions were absent or only mild in 6 of the 8 patients. Most patients in remission managed to fully taper off their concomitant steroid treatment.

An extension of this original trial\textsuperscript{57} comprised a total of 24 patients treated with 10 \(\mu\)g/kg visilizumab. On day 30, clinical improvement was observed in 84% (19 of 24) of these patients (Modified Truelove and Witts Severity Index, <10), remission was observed in 66%, and endoscopic remission was observed in 44%. After 1 year, 10 of 22 patients did not require surgical or medical salvage therapy. Colectomies were performed for intractable colitis in 7 patients during long-term follow-up evaluation. The median time to colectomy was 160 days (range, 13–410 days). However, a phase III, randomized, double-blind, placebo-controlled, multicenter study of visilizumab in subjects with intravenous steroid-refractory ulcerative colitis was withdrawn and the visilizumab clinical development program for treatment of ulcerative colitis and Crohn’s disease was terminated because an interim analysis showed no difference in colectomy rates for visilizumab vs placebo.
One co-stimulatory pathway of T-cell activation involves the interaction between CD40 and CD40L. Ch5D12 is a chimeric IgG4 antibody to CD40. Its effects were tested in 18 patients with Crohn’s disease in a phase I/IIa trial. Response and remission rates of 72% and 22%, respectively, are difficult to interpret without placebo controls, but more studies appear to be justified. It seems to be more logical to target CD40L, however, because this type II integral membrane glycoprotein is expressed on activated T cells.

Another co-stimulatory signal required for full T-cell activation occurs through interaction between the CD28 protein on the T-cell surface and the B7 protein (CTLA-4) on the antigen presenting cell. Abatacept is a protein that contains a high-affinity binding site for B7 and inhibits the co-stimulatory signal to T cells, thus preventing the full activation of T cells. It is effective in treating patients with rheumatoid arthritis and phase III trials currently are underway to test its effects in patients with Crohn’s disease and ulcerative colitis.

CD25 (IL-2 receptor) is a membrane receptor expressed by activated T lymphocytes. IL-2 is a cytokine produced by T cells that induces lymphocyte proliferation and differentiation (clonal expansion); its overproduction is associated with a variety of immune disorders. The calcineurin inhibitor cyclosporin, which inhibits IL-2, is effective for the treatment of severely active ulcerative colitis. Therefore, it was proposed that blocking IL-2 receptor would be an effective therapy for ulcerative colitis.

Daclizumab (zenapax; Protein Design Labs), a humanized IgG1 monoclonal antibody to CD25 (IL-2R), and basiliximab (Simulect; Novartis, Basel, Switzerland), a chimeric anti-CD25 monoclonal IgG1 antibody, are under development for the treatment of ulcerative colitis. The effects of daclizumab were tested in an open-label pilot trial in 10 patients. Patients were given 2 intrave-

Figure 4. Therapeutic proteins that affect T-cell proliferation and activation can act at different molecular levels. Visilizumab blocks the binding of antigen presenting cell major histocompatibility complex-II molecules with the T-cell receptor or CD-3, resulting in apoptosis of T cells. The co-stimulatory molecules B7 and CD-28 also are essential for T-cell activation; blocking their interaction with the CLTA-4/Fc-fusion protein abatacept results in T-cell anergy. The anti-CD25 (α-chain of the activated IL-2 receptor) mAbs basiliximab and daclizumab prevent IL-2 receptor signaling and downstream T-cell activation and proliferation.
nous doses (1 mg/kg) with a 4-week interval between doses. Promising response rates were observed by 8 weeks. Subsequently, a randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of daclizumab (induction therapy) in patients with active ulcerative colitis. A total of 159 patients with moderate ulcerative colitis were assigned randomly to groups that were given intravenous 1-mg/kg doses of daclizumab at weeks 0 and 4; 2-mg/kg doses at weeks 0, 2, 4, and 6; or placebo. At week 8, remissions were observed in 2% of patients receiving daclizumab 1 mg/kg ($P = .11$ vs placebo) and 7% of patients receiving 2 mg/kg ($P = .73$), compared with 10% of those who received placebo. Responses occurred at week 8 in 25% of patients receiving daclizumab 1 mg/kg ($P = .04$) and in 33% of patients receiving 2 mg/kg ($P = .30$) compared with 44% of those receiving placebo. Basiliximab was evaluated only in open-label pilot trials and the data might show efficacy, but we await the results of a larger, placebo-controlled trial. However, data from clinical trials with daclizumab and basiliximab do not suggest that there is a role for anti-CD25 antibodies in the treatment of ulcerative colitis.

**Stimulation of the Innate Immune System**

The innate immune system involves cells and mechanisms that defend the host from infection by organisms in a nonspecific manner. Cells of the innate system recognize and respond to pathogens in a generic way and provide immediate defense against infection. The major functions of the innate immune system include activation and recruitment of immune cells to sites of infection and inflammation, activation of the complement cascade, and promotion of the clearance of dead cells or foreign material by specialized white blood cells. Antigen presentation is the first step in the adaptive immune response.

**Growth Factors**

Sargramostim (GM-CSF) (Leukine, Berlex; Bayer Healthcare Pharmaceuticals, Montville, NJ), a hematopoietic growth factor, stimulates cells of the intestinal innate immune system. Preliminary studies suggested that sargramostim may have activity in Crohn’s disease by stimulating the innate immune system. A randomized, placebo-controlled trial was performed in 124 patients with moderately-to-severely active Crohn’s disease; patients were given sc injections of 6 μg/kg sargramostim or placebo for 56 days. At the end of treatment (day 57), no significant difference in the rate of a clinical response, defined by a decrease of at least 70 points in the CDAI score, was observed between the groups given sargramostim or placebo (54% vs 44%; $P = .28$). However, significantly more patients in the sargramostim group, compared with the placebo group, reached the 100-point clinical response defined (48% vs 26%; $P = .01$) and achieved remission (CDAI, <150) (40% vs 19%; $P = .01$). Mild-to-moderate injection-site reactions and bone pain were observed commonly in the patients given sargramostim.

In a large phase III placebo-controlled trial of 286 patients (NOVEL 4), patients (2:1 ratio) were given sc injections of 6 μg/kg/day sargramostim or placebo for 56 days. No differences between groups were found in remission and response rates at day 56. The development of sargramostim for the treatment of Crohn’s disease has been halted.

Several epithelial growth factors have been evaluated for the treatment of ulcerative colitis. Epithelial growth factors are naturally occurring proteins capable of stimulating cellular growth, proliferation, and cellular differentiation. Growth factors are important for regulating a variety of cellular processes.

In ulcerative colitis, the inflammation and epithelial necrosis are confined to the mucosa, and epithelial cell damage is an important feature. The effects of the keratinocyte growth factor-2 Repifermin (Human Genome Sciences, Rockville, MD) were studied in a phase II, placebo-controlled trial in patients with moderately active ulcerative colitis. Intravenous doses of 1–50 μg/kg were well tolerated, but there was no evidence of efficacy. In a separate placebo-controlled trial, patients with mild-to-moderate ulcerative colitis were given 5 μg of epidermal growth factor, via enema, in combination with oral mesalamine. After 2 weeks, 10 of the 12 patients (83%) given the epidermal growth factor enemas were in remission compared with 1 of the 12 patients (8%) given placebo.

Further studies are warranted but safety of therapies stimulating epithelial cell growth in ulcerative colitis, a disease that predisposes to colorectal cancer, is of concern. Promising results also have been reported with somatostatin for the treatment of Crohn’s disease, but follow-up studies have not been reported.

**Small Molecules That Target Immune Pathways**

Small molecules already are used widely in the treatment of IBD. Examples are mesalamine, azathioprine/6-mercaptopurine, and methotrexate. The mechanism of action of these drugs is poorly understood. Recently, a large number of small molecules that target specific immune pathways were studied for the treatment of IBD. There are a number of important problems associated with the use of these drugs. In contrast with monoclonal antibodies, small molecules rarely completely are specific for one pathway. Moreover, they do not completely block a single molecule like the monoclonal antibodies do.

Several mitogen-activated protein kinase inhibitors, including semapimod and doramapimod, which inhibit the production of TNF, have been tested in clinical trials in Crohn’s disease. Although an early open-label trial with semapimod gave promising results, a placebo-
Table 2. Monoclonal Antibodies and Constructs in the Treatment of IBD

<table>
<thead>
<tr>
<th>Target</th>
<th>Compound</th>
<th>Manufacturer</th>
<th>Stage of development</th>
<th>Disease</th>
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<td>CD, UC/CD, UC</td>
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<td>Abbott</td>
<td></td>
<td>CD, UC</td>
<td>CD/CD</td>
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<td>UCB</td>
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<td>CD/–</td>
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<td>UC</td>
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</table>


controlled trial did not show efficacy in the short term. The results of the trial have not yet been published. Also, doramapimod was not effective in the setting of a placebo-controlled trial. Another small molecule, RDP58, has topical thalidomide-like activity, inhibiting proinflammatory cytokines including TNF. A pilot trial suggested activity in the treatment of ulcerative colitis, but we await the results of a placebo-controlled trial.

Peroxisome proliferator-activated receptor gamma (PPARγ) agonists are expected to have beneficial effects in IBD. Rosiglitazone is a selective ligand of PPARγ, and has no PPARα-binding action and is used as an antidiabetic drug. Rosiglitazone has been shown to have promising effects in patients with mild to moderately active ulcerative colitis, but because its action seems similar to that of mesalamine.

The development of apilimod mesylate, a small-molecule inhibitor of the transcription of IL-12/IL-23, was halted for the treatment of Crohn's disease after a phase II dose-escalation study did not show efficacy. Several small-molecule inhibitors of adhesion molecules are under study, but the development of drugs that inhibit the integrin α4 subunit has been slowed by the PML that developed in patients who took natalizumab.

CCX282 (Traficet-EN; ChemoCentrxy, Mountain View, CA) is a highly potent antagonist of CCR9, a G-protein-coupled chemokine receptor that is expressed on most T cells in the intestine. The ligand is CCL25, also called thymus-expressed chemokine, present mainly in the small intestinal epithelium. Traficet-EN is designed to prevent migration of T cells to the intestine. In a phase II trial, 74 patients with Crohn's disease were given either a once-daily 250-mg capsule of Traficet-EN or placebo for 28 days. The CDAI scores and CRP levels were measured at baseline and on study days 8, 15, and 29. Traficet-EN showed clinical benefit. Of patients in the Traficet-EN group, 58% had a reduction in CDAI scores greater than or equal to 70 points, compared with 31% of those given placebo. Importantly, Traficet-EN's anti-inflammatory activity was shown by a decrease in CRP levels in patients given the small molecule. The full results of this trial have not yet been published; another phase II trial is underway. The placebo-controlled induction phase of this trial has been completed but the results have not yet been disclosed.

Safety of Biological Therapies

Biological therapeutics have a number of safety issues that differ from those of standard drugs such as sulfasalazine, mesalamines, steroids, and even azathioprine and methotrexate. Moreover, biologics frequently are given to patients who were refractory to the former treatments and frequently are added to these standard drugs. Therefore, patients may experience cumulative toxicities of the different medications. One of the main concerns are opportunistic infections (besides reactiva-
tion of tuberculosis) and malignancies, especially lymphoma, that arise. Specific adverse events seem to occur with certain drugs or combinations of drugs, such as the cases of PML in patients who were given natalizumab, or hepatosplenic T-cell lymphoma\textsuperscript{73} in patients who were given a combination of azathioprine and infliximab. Physicians who treat patients with biologic therapies should be aware of the possible safety problems of each of the therapies and the ways to avoid and treat them.

Furthermore, patients frequently develop an antibody response against biological drugs. The immunogenicity is different for each drug and the importance is not well understood for most of the molecules. It is clear that antibodies can interfere with the pharmacokinetics of the drug and hence with its effects. They can be the cause of acute and delayed infusion reactions and also of injection site reactions. Clinicians should be aware of the safest and most effective ways to administer these therapeutics to minimize the problems associated with antibody formation.

The Future of Biological Therapies

Anti-TNF agents allow a more profound control of the bowel inflammation that results in mucosal healing, compared with conventional therapies, which could translate into improvement of long-term outcome of the disease course. There are already preliminary data showing that infliximab therapy decreases the need for hospitalizations and surgery in patients with luminal or fistulizing Crohn’s disease\textsuperscript{17,18}; similar data are available for adalimumab.\textsuperscript{74} This has led to the concept that the traditional step-up introduction of therapies may not be the optimal way to treat patients. There are data that suggest that treatment with anti-TNF agents can avoid the use of steroids and might be used to bridge the delayed effect of immunosuppressives.\textsuperscript{41,73} However, there is not sufficient proof that the early use of anti-TNF therapies slows the progression of Crohn’s disease.

To avoid immunogenicity problems, new antibodies have been designed including avimers and nanobodies. Avimer proteins are multimeric binding proteins or peptides engineered using in vitro exon shuffling and phage display. Multiple binding domains are linked, resulting in greater affinity and specificity compared with single-epitope domains. Nanobodies (also known as single-domain antibodies or V\textsubscript{H}H antibodies) are about a tenth the size of human antibodies and just a few nanometers in length. They are fully functional antibodies but lack light chains. These molecules have to be studied in clinical trials to determine whether they are suitable candidates for treatment of IBD. A phase I study on the safety of avimers binding IL-6 receptor in Crohn’s disease currently is ongoing.

Most biological therapies seem to be effective in both Crohn’s disease and ulcerative colitis, although they were not all developed for both indications. This seems to suggest that there are more similarities in the pathogenesis of these diseases than differences.

The most important unmet need is to develop treatment modalities that are efficacious in patients who do not respond to a first biological drug. This implies the identification of predictive factors for response to each of the existing classes of molecules. Completely different approaches, including the induction of tolerance with biological molecules such as CTLA4-Ig, currently also are being investigated. Topical administration of IL-10, trefoil factors, nanobodies, and other molecules now are possible using genetically modified \textit{Lactococcus lactis} and represent exciting new approaches to therapy of IBD. Furthermore, alternative treatment approaches, such as autologous hematopoietic stem cell transplantation for patients with very severe disease, are under investigation.

Recent progress in IBD genetics has advanced our understanding of IBD pathogenesis substantially, especially for Crohn’s disease, and suggested many new potential pathways. Functional analysis of these pathways will lead to better understanding also of the interaction between genes and the environment in IBD. The improved understanding of pathogenic mechanisms and the basis of heterogeneity within the disease groups should lead to different therapeutic approaches for various disease phenotypes and eventually to personalized treatment. It needs to be said, however, that discovery of any of the genes identified to be involved in susceptibility to IBD has led to a new therapeutic approach so far.

References


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Reprint requests
Address requests for reprints to: Paul Rutgeerts, MD, PhD, FRCP, AGAF, Division of Gastroenterology, University of Leuven Hospitals, Herestraat 49, 3000 Leuven, Belgium. e-mail: paul.rutgeerts@uz.kuleuven.ac.be; fax: (32) 16344419.

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