ABSTRACT

Crohn’s disease (CD) affects approximately 500,000 Americans, usually striking between the ages of 15 and 35 years. Before 1998, when the first tumor necrosis factor (TNF)-α antagonist was approved for the treatment of CD, therapy consisted of aminosalicylates and corticosteroids to reduce inflammation, immune modifiers or modulators to reduce corticosteroid requirements, and antibiotics to treat perianal lesions. Although these standard agents are still widely used with or without TNF-α antagonists, ongoing research is focused on additional biologic agents that target TNF-α and other cytokines and molecules that are involved in inflammation. This article reviews standard CD therapies and then explores current treatment approaches in greater detail, with emphasis on the role of TNF-α in CD, the clinical use of TNF-α antagonists in general, and the unmet needs and challenges of therapy with these agents. The article also discusses recent and ongoing research on other agents for the treatment of CD, including interleukin-12 antagonists, interferon-γ antagonists, adhesion molecule antagonists, growth hormone, thalidomide, and Trichuris suis ova.


Although no existing pharmacologic agent can induce remission in all patients with Crohn’s disease (CD), recent research efforts exploring the etiology and pathophysiology of CD have led to the development of new therapies that have benefited many patients. For example, the approval of a tumor necrosis factor (TNF)-α antagonist for induction of remission in 1998 marked a major advance in CD therapy by providing a treatment option that effectively targeted an underlying mechanism of inflammation in this condition. Continuing research focusing on this class of drugs and other biologic and nonbiologic agents with antiinflammatory activity suggests that at least one TNF antagonist may be available soon and that additional therapeutic options may be available in the future.

OVERVIEW OF CROHN’S DISEASE

Crohn’s disease, which was first described in the literature in 1932, is a chronic disabling disorder that causes inflammation of the gastrointestinal (GI) tract. Chronic inflammation represents an abnormal response by the body’s immune system, which mistakes protective commensal bacteria for foreign invaders and launches an attack by dispatching white blood cells into the lining of the intestine. In addition to chronic inflammation, these cells also generate a host of harmful substances that ultimately lead to intestinal ulcerations, bowel injury, and the characteristic symptoms of CD. Crohn’s disease, which affects approximately 500,000 Americans, strikes males and females equally, usually between the ages of 15 and 35 years. However, it can occur at any age. Approximately 10% are children and adolescents younger than the age of 18 years, and a smaller percentage are older than the age of 70 years when they first develop symptoms.
Crohn’s disease is thought to be caused by an interaction between an extrinsic agent, such as a virus or a bacterium, and the immune system that triggers the disease, or by the damaging effects of the extrinsic agent per se to the intestinal wall. Genetic factors clearly play a role. Approximately 20% of patients with CD or ulcerative colitis (UC), a related inflammatory disease, have a close relative with either disease. Risk for CD or UC is 10 times that of the general population in those with a relative with either disease, and 30 times that of the general population if the relative is a sibling.

Race, ethnicity, and environment also appear to play a role. American Jews of Eastern European descent (Ashkenazi Jews) are 4 to 5 times more likely to develop CD or UC than the general population, and the prevalence of both is highest among whites (149/100,000) and lowest among Asians and Hispanics. In contrast, the once-low number of reported cases of CD and UC among African Americans has been increasing steadily in recent years.

Crohn’s disease and UC are far more common in industrialized nations, primarily the United States and Europe, than in less developed areas of the world. The reasons for these disparities are not yet clearly understood.

Symptoms and complications vary in accordance with the type of CD and the area of the GI tract that is inflamed. Symptoms, which can range from mild to severe and can alternate between flare-ups and remissions, include diarrhea, abdominal pain, cramping, rectal bleeding, loss of appetite, weight loss, nausea, vomiting, and fatigue. Involvement of the joints, eyes, skin, and liver may also be present. Complications include intestinal obstruction due to edema and the formation of scar tissue producing fibrotic strictures, ulcers within the GI tract, and fistulas, which affect approximately 30% of patients with CD. Fistulas may extend beyond the intestine to surrounding tissues, such as the bladder, vagina, and skin, or they may form abscesses.

Other complications include malnutrition, malabsorption of dietary protein, fat, carbohydrates, and water, and protein, fat, and vitamin deficiencies. Although there is no evidence that any particular foods cause or contribute to CD, paying special attention to diet, particularly during episodes of disease flares, may help reduce symptoms, replace lost nutrients, restore lost weight, and promote healing.

At present, approximately 65% to 75% of patients with CD require surgery at some point, either because pharmacologic agents can no longer control symptoms, there is a fistula or fissure that requires repair, there is an intestinal obstruction or abscess, or the colon is diseased and requires resection. It is hoped that recent and emerging CD therapies with enhanced anti-inflammatory efficacy and the ability to modify disease will provide improved control of symptoms, induce and maintain remission without serious side effects, promote healing, reduce the development of complications, and ultimately obviate the need for surgery.

**HISTORICAL APPROACH TO TREATMENT**

Until 1998, when infliximab became the first biologic agent to be approved for the treatment of CD, standard therapies for CD included systemic and topical corticosteroids, oral and rectal 5-aminosalicylic acid (5-ASA) compounds, and immunosuppressant or immunomodulatory agents, such as azathioprine (AZA) or its metabolite 6-mercaptopurine (6-MP), methotrexate, and cyclosporine. Other standard therapies included antibiotics, such as metronidazole and the quinolones to treat fistulas, abscesses, and bacterial overgrowth resulting from strictures and blind loops of intestine; antidiarrheal and antispasmodic agents to treat acute symptoms; and nutritional support with elemental and polymeric dietary formulas and/or prebiotic and probiotic agents when necessary.

Although these standard therapies remain an integral part of current clinical management of CD, they are associated with a number of important limitations. Steroids, for example, do not modify disease or heal the mucosa, and they produce significant short- and long-term side effects. Immunosuppressants, by comparison, modify disease but work too slowly to be useful in inducing remission. As such, these therapies underscore the need for more effective treatments that would overcome these limitations and also meet the challenges of managing a chronic and complex disease, such as CD.

**CORTICOSTEROIDS**

Historically, oral corticosteroids have long been the mainstay of therapy to reduce inflammation and induce remission. Although they have been shown to induce remission in 48% of patients with active CD and ameliorate symptoms in an additional 32% within the first 30 days of treatment, 20% of patients are resistant to these agents from the outset. Moreover, 45% of those with a favorable initial response become steroid-
dependent by 1 year. Other studies have shown that only 32% of patients with CD have a prolonged response at 1 year to a first course of steroid therapy, suggesting that these agents do not modify disease despite their ability to induce remission and relieve symptoms in a substantial proportion of patients.

The high incidence and serious nature of the short-term side effects and long-term toxicity of systemic corticosteroids (Table 1) raised serious concerns and led to the development of topical steroids such as budesonide, which was introduced in 1994. Although budesonide is somewhat less effective than oral prednisolone in inducing remission, it has significantly fewer side effects and a less pronounced effect on suppression of the hypothalamic-pituitary-adrenal axis. Although budesonide and other topical steroids can be used for longer periods of time than oral steroids, thereby prolonging the time to relapse, they have not been demonstrated to be effective in maintaining remission.

**Aminosalicylates (5-ASA Compounds)**

Aminosalicylates, which have anti-inflammatory properties, are commonly used to treat CD even though the evidence in support of their use for this indication is not robust. Sulfasalazine, which has been available since 1979, is modestly effective in treating active Crohn’s colitis and ileocolitis, and oral and rectal formulations of 5-ASA, which were introduced in 1993, are only slightly more effective than placebo in treating mildly to moderately active CD. Neither sulfasalazine nor any of the 5-ASA compounds is effective in maintaining remission after corticosteroid therapy.

**Antibiotics**

Antibiotics are considered by some to be a potential alternative to corticosteroids despite scant evidence from controlled studies that they are useful in this regard. However, antibiotics such as metronidazole and the quinolones are useful in treating complications, such as fistulas and abscesses and in reducing bacterial overgrowth resulting from strictures and blind loops in the intestine.

Metronidazole has been evaluated as therapy for CD since 1975. One placebo-controlled trial demonstrated that 2 different doses of the drug (20 mg/kg and 10 mg/kg) significantly decreased Crohn’s Disease Activity Index (CDAI) scores compared to placebo, with the beneficial effect being most pronounced in patients with ileocolonic disease. However, high-dose metronidazole is associated with side effects, such as peripheral neuropathy, which can take months to resolve after the drug is discontinued or may be permanent, and general intolerance, such as metallic dysgeusia and GI upset.

**Immunomodulators/Immunosuppressants**

Unlike corticosteroids, which have a rapid onset of action, immunomodulating or immunosuppressive agents, such as AZA/6-MP and methotrexate, have a slow onset of action and are thus not useful in inducing rapid remission. However, they are effective in maintaining remission. They are also used to treat fistulizing CD, although fewer than 50% of these patients exhibit a complete response.

In a placebo-controlled study, 42% of patients treated with AZA (vs 7% of those receiving placebo) were still in remission 15 months after remission was initially induced by corticosteroids. In contrast to a retrospective study showing that the effects of AZA in maintaining remission decline over time, a more recent prospective randomized controlled trial found that 18 months of continued therapy with AZA was superior to placebo in prolonging remission even further in patients who were already in clinical remission after induction with AZA for 42 months or longer.
However, approximately 15% of patients are unable to tolerate AZA/6-MP, which has been available since 1980, largely because of nonspecific nausea or malaise.3

Interestingly, AZA/6-MP appears effective in children with CD of recent onset.3 As reported in one study, the remission rate at 1 year was 85% with 6-MP 1.5 mg/kg (after induction of remission with steroids over 3 months) versus 54% with placebo in children with steroid-dependent active CD.15

Methotrexate, an immunomodulating antimetabolite long used in treating certain forms of cancer, in addition to immune-mediated diseases such as asthma, psoriasis, and rheumatoid arthritis, has been used in the treatment of CD since 1995.3 In one study, a weekly intramuscular (IM) dose of 25 mg induced remission at 12 weeks in 39% of patients with chronically active CD that failed to respond to at least 3 months of steroid therapy, prompting the investigators to suggest methotrexate as an alternative to AZA/6-MP.16 In a follow-up report, the investigators noted that weekly IM injections of methotrexate 15 mg maintained the remission induced by the 25-mg dose in 65% of the patients versus 39% of patients receiving placebo.17

Findings from other studies were similar. A review of 3 randomized, placebo-controlled trials found that high-dose weekly methotrexate (25 mg IM) was effective in inducing remission within 16 weeks in patients with refractory CD, but that lower IM doses were not.18 Moreover, a study assessing the long-term efficacy and toxicity of weekly maintenance therapy with low-dose methotrexate (<25 mg) for a median of 18 months suggested long-term benefit with generally moderate side effects in patients with chronically active CD.19

Although oral methotrexate has been used with great success in patients with rheumatoid arthritis and psoriasis for the past 50 years, data on its use in CD are sparse and controversial.20 In a randomized, double-blind, placebo-controlled study, oral methotrexate 15 mg/week showed a trend toward fewer CD flares versus placebo, along with a higher number of significant side effects.21 However, oral methotrexate has not been adopted as a standard of care in CD; in most cases, parenteral delivery, IM or subcutaneously, is the method of choice.

The most common side effects associated with AZA/6-MP and methotrexate are summarized in Table 2.

Cyclosporine was first used to prevent rejection in organ transplantation. Because it was found to be effective and well tolerated in this setting, and subsequently in patients with autoimmune diseases, it was also investigated in CD.22 After early, open studies reported that oral cyclosporine was effective in inducing remission in CD, 4 randomized controlled trials were done to ascertain whether the results of the open studies were valid.22 As noted in a systematic review of these trials, only one (by Brynskov et al) found that high-dose oral cyclosporine was significantly better than placebo in inducing clinical improvement, but not remission, at 12 weeks.22-23 The authors of the review concluded that low-dose oral cyclosporine does not appear to be justified in the treatment of chronic active CD, and that higher oral doses and parenteral administration of the drug have not been adequately evaluated in controlled trials.

Although a 12-month placebo-controlled trial, in which patients also received steroids, with the dosage determined by CDAI score, found that a higher proportion of patients receiving cyclosporine achieved a full remission at 4 months (35% vs 27%), only 20% of patients maintained a continuous remission at 12 months.24 Moreover, long-term cyclosporine plus low-dose steroids was not superior to low-dose steroids alone. Open-label studies have found that intravenous (IV) cyclosporine rapidly and effectively produces improvement in patients with acute, steroid-refractory flare-ups and fistulizing CD.25-27

Potentially serious complications associated with cyclosporine use, and its general lack of long-term efficacy in CD, have led to its being abandoned as a treatment for CD, with infliximab having taken its place in the armamentarium. The most common side effects associated with cyclosporine are summarized in Table 2.

### Table 2. Side Effects of Immunomodulators/Immunosuppressants

<table>
<thead>
<tr>
<th>Azathioprine/6-MP</th>
<th>Methotrexate</th>
<th>Cyclosporine</th>
</tr>
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<tbody>
<tr>
<td>Myelosuppression</td>
<td>Myelosuppression</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>Opportunistic infections</td>
<td>Hepatic fibrosis</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Interstitial pneumonitis</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Increased risk of lymphoma</td>
<td>Teratogenicity</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td>Malaise</td>
<td></td>
<td>Seizure</td>
</tr>
</tbody>
</table>

6-MP = 6-mercaptopurine.
**Tacrolimus**

A randomized controlled trial of tacrolimus in fistulizing CD demonstrated short-term closure of fistulas. However, treatment was associated with many dose-limiting side effects. This agent could be considered as an alternative for patients with fistulas who may have failed infliximab, but routine use is limited by its overall toxicity profile and poor tolerance.

**Current Approach to Treatment**

The current approach to the treatment of CD reflects the considerable improvements in medical therapy in recent years, particularly the introduction of infliximab and further study of older drugs to advance the clinician’s ability to devise the optimum therapeutic regimen for individual patients with regard to benefits, adverse effects, and dosing.

At present, most patients with CD are initially treated with standard therapies. The majority continue to be also treated with standard therapies, with or without infliximab, which has thus far been used in an estimated 20% to 30% of patients with CD. However, current thinking is leaning toward the approach used in rheumatoid arthritis: treat early and aggressively to induce and maintain remission and prevent disease progression. Preliminary results from a randomized controlled trial in patients with moderately to severely active CD of less than 4 years’ duration support this approach. In that trial, a regimen of infliximab and AZA was found to be superior to step-up steroid therapy in inducing remission.

**Role of TNF in Crohn’s Disease**

Before discussing the TNF-α antagonists as a class and the clinical experience with these agents to date, it is worth reviewing the role of TNF in CD. Unlike other cytokines in the inflammatory cascade, TNF has numerous and diverse physiologic effects in a variety of animal models and in humans. It is present in significantly higher amounts in the stool and mononuclear cells isolated from the lamina propria of patients with CD, and is critical in the formation of granulomas, a frequent finding in patients with CD.

However, what is most notable about TNF is its broad range of pro-inflammatory effects and, thereby, its central role in the regulation of inflammation in CD and other inflammatory diseases. TNF induces the secretion of several pro-inflammatory cytokines and chemokines from stromal, endothelial, and mucosal mononuclear cells. It can also bind to either of its 2 receptors, both of which are capable of activating nuclear factor kappa B, a pro-inflammatory transcription factor, through distinct intracellular signaling pathways. The result is increased production of interleukin (IL)-1 and IL-6, 2 other pro-inflammatory cytokines, and activation of macrophages and dendritic cells, which in turn secrete more TNF.

In addition, TNF induces mucosal T cells to increase production of interferon (IFN)-γ. Together, TNF and IFN-γ loosen the tight junctions between epithelial cells, a process that may cause apoptosis of these cells and lead to diminished mucosal barrier functions. TNF also induces stromal cells in the lamina propria to produce matrix metalloproteinases, which directly injure surrounding tissues, and provokes the increased expression of various adhesion molecules from the endothelial cells, which contributes to leukocyte recruitment from the peripheral circulation and amplifies the nascent inflammatory response. Another effect of TNF is the production of chemokines and chemokine receptors, which contributes to recruitment of leukocytes and activation of immature dendritic cells, which then migrate to regional lymph nodes to bolster the adaptive immune response even further.

**TNF-α Antagonists**

The multitude of pro-inflammatory effects of TNF and its central role in the regulation of inflammation in CD indicate that physiologic control of TNF expression is amenable to therapeutic regulation at numerous points in the inflammatory process with agents such as TNF antagonists. Indeed, studies demonstrating the efficacy of infliximab in inducing and maintaining remission, reducing corticosteroid requirements, and healing fistulas in CD spurred the development of other anti-TNF agents. Thus far, 6 agents in this class have been or are being studied in patients with CD or UC (Table 3), with some variability in efficacy.

Although infliximab and adalimumab have been shown to be effective in inducing remission in active CD, CDP571 has been shown to be only moderately effective in this regard. However, both CDP571 and certolizumab pegol (CDP870) have discernible efficacy in inducing remission in the subset of patients with elevated levels of C-reactive protein (CRP), although...
preliminary results of a 26-week, phase III study of certolizumab pegol have shown that it induced and maintained remission in patients with moderate to severe CD regardless of CRP level.31,37 Onercept has failed to demonstrate efficacy in CD in phase II trials,36 and etanercept has proved to be ineffective in CD when used at the same doses that are highly effective in rheumatoid arthritis.31,38

Post hoc analyses of early studies with CDP571 and certolizumab pegol suggested that these agents may be more efficacious in patients with elevated CRP, whereas other agents have been effective in unselected populations of patients with CD. This raises questions about what factors might account for the differences. Two explanations for the efficacy of CDP571 and certolizumab pegol in patients with high CRP levels—patients with low levels have symptoms that are driven by factors other than inflammation or that patients with high levels have symptoms that are specifically driven by TNF—suggest that an agent’s ability to neutralize TNF is not enough to make it an effective anti-TNF agent.31

Factors other than inflammation that may explain differences in efficacy include differences in inducing T-cell apoptosis, which is defective in CD; whether an agent weakly or strongly binds membrane-bound TNF; and differences in inhibition of TNF signaling.31

Also of interest is RDP58, a novel nonbiologic agent that inhibits the synthesis of pro-inflammatory cytokines by disrupting cell signaling. Parallel multicenter, randomized, double-blind, placebo-controlled concept studies in patients with mild to moderate UC have shown that oral RDP58 200 mg or 300 mg, but not 100 mg, is effective in reducing the simple clinical colitis activity index score and is well tolerated, with the incidence of adverse effects no different from that seen with placebo.39

**UNMET NEEDS AND CHALLENGES**

In addition to the major unmet need of medical therapy of CD (ie, the lack of a curative drug or drugs for all patients with the disease), there are several unmet needs and clinical challenges associated with anti-TNF agents. These include loss of response, immunogenicity, serious adverse events, bothersome adverse events related to the IV or subcutaneous administration of these drugs, and lack of data regarding the use of some of these agents in patients with CD.

Although infliximab has demonstrated efficacy in inducing and maintaining response and remission in patients with active and fistulizing CD, some patients who responded to the drug initially have

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**Table 3. Anti-TNF Agents Evaluated for Treatment of CD**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase of Investigation</th>
<th>Induction of Remission</th>
<th>Maintenance of Remission</th>
</tr>
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<tbody>
<tr>
<td>Infliximab*</td>
<td>IV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adalimumab†</td>
<td>III</td>
<td>Yes</td>
<td>Phase III trials under way</td>
</tr>
<tr>
<td>Certolizumab pegol (CDP870)</td>
<td>III</td>
<td>Yes</td>
<td>Yes‡</td>
</tr>
<tr>
<td>CDP571</td>
<td>III (failed)</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Etanercept†</td>
<td>II (failed)</td>
<td>No</td>
<td>No data</td>
</tr>
<tr>
<td>Onercept</td>
<td>II (failed)</td>
<td>No</td>
<td>No data</td>
</tr>
</tbody>
</table>

* Approved for CD and rheumatoid arthritis.
† Approved for rheumatoid arthritis.
‡ Preliminary data from a phase III trial.
CD = Crohn’s disease; Ig = immunoglobulin; TNF = tumor necrosis factor.
Based on data from Sands; Sandborn; and Schreiber et al.
experienced loss of response during maintenance therapy. Increasing the maintenance dose up to 10 mg/kg or reducing the dosing interval may restore the response. Although a large phase III trial evaluating adalimumab in patients with active CD who have lost response to infliximab is under way, data on loss of response to certolizumab pegol and CDP571 are unavailable.

Immunogenicity, or the formation of antibodies, is clinically relevant because it increases the rate of infusion reactions and loss of efficacy. Antibodies to infliximab have been reported in 30% to 75% of patients who receive the drug episodically without a concomitant immunosuppressant. Treatment strategies to reduce the incidence of antibodies to infliximab include a 3-dose induction regimen over 6 weeks, followed by systematic maintenance dosing at 8-week intervals, concomitant immunomodulator therapy with AZA, 6-MP, or methotrexate, and pre-treatment with IV hydrocortisone.

Although there are no available data on the immunogenicity of adalimumab in patients with CD, data from rheumatoid arthritis studies indicate that antibodies to the drug are present in 5% of patients, with rates ranging from 1% in those receiving concomitant methotrexate to 12% in those receiving adalimumab alone.

In one clinical trial involving patients with CD, antibodies to CDP571 were present in 11%, with rates ranging from 5% in patients receiving concomitant AZA, 6-MP, or methotrexate to 14% in patients receiving CDP571 alone. However, there are no available data on antibody formation rates in patients with CD for certolizumab pegol, etanercept, or ontercept.

In general, the TNF antagonists are well tolerated by most patients. However, significant adverse events can occur, including acute infusion or injection-site reactions, delayed hypersensitivity reactions, demyelination, drug-induced lupus, and increased risk for serious and opportunistic infections and non-Hodgkin’s lymphoma. All of these events have been documented in patients with rheumatoid arthritis receiving adalimumab.

Further investigations to identify the most appropriate dosing schedules and the best sequence of TNF antagonists, immunomodulators, and other drugs are needed to minimize loss of response, immunogenicity, and adverse events, improve remission rates, and promote complete healing of the mucosa.

**Investigational Therapies**

Several agents targeting various components of the inflammatory cascade and the immune system, in addition to other novel therapies, have recently been or are currently being studied for their potential clinical use in CD. These agents include IL-6 and IL-12 antagonists, anti-IFN-γ antibodies, anticellular adhesion molecule antibodies, colony-stimulating factors, and a novel therapy involving exposure to helminths.

**IL-6 and IL-12 Antagonists**

The efficacy of tocilizumab (ie, MRA), a humanized monoclonal antibody against the IL-6 receptor, was evaluated in a 12-week phase II study involving 36 patients with active CD. Tocilizumab was found to be effective in inducing response and remission in patients receiving 8 mg/kg IV every 2 weeks, but not in those receiving the same dose every 4 weeks. When levels of IL-12 are increased, as they are in CD, they lead to increased production of TNF-α and IFN-γ, thus making IL-12 an attractive therapeutic target. ABT-874, a fully human immunoglobulin (Ig) G1 monoclonal antibody against IL-12, has been found to down-regulate IL-12 secretion in patients with active inflammation. A phase II study, in which 79 patients with active CD were administered ABT-874 1 mg/kg or 3 mg/kg for 7 weeks, found that the higher dose was effective in inducing response and remission. STA-5326, an oral inhibitor of IL-12, is being explored in active CD.

**Anti-IFN-γ Antibodies**

The increased production of IFN-γ resulting from increased concentrations of IL-12 also makes IFN-γ a therapeutic target. Thus far, one humanized IgG1 monoclonal antibody against IFN-γ, fontolizumab, has been evaluated in a phase II study involving 133 patients with moderate to severe CD. Although patients given fontolizumab 4 mg/kg IV or 10 mg/kg IV at week 0 failed to achieve the primary endpoint—response at week 4—a subgroup analysis revealed that the drug induced a response in patients with elevated CRP levels at baseline who were given a second dose at week 4. In addition, the drug was well tolerated.

**Anticellular Adhesion Molecule Antibodies**

Adhesion molecules represent another target that may be amenable to therapeutic intervention. Agents
with activity against adhesion molecules include natalizumab, a humanized IgG4 monoclonal antibody against the cellular adhesion molecule α4 integrin; MLN-02, a humanized IgG1 monoclonal antibody to α4β7 integrin; and alicaforsen, an intercellular adhesion molecule-1 antisense oligodeoxynucleotide.

Natalizumab inhibits leukocyte adhesion and migration into inflamed tissues. Because it also inhibits leukocyte migration to the central nervous system, it has been evaluated in patients with multiple sclerosis and in patients with CD. A double-blind, placebo-controlled trial conducted by the Natalizumab Pan-European Study Group in 248 patients with moderate to severe CD found that the drug (3 mg/kg IV or 6 mg/kg IV at weeks 0 and 4) increased the rates of response and clinical remission, improved quality of life, decreased CRP levels, and was well tolerated. Increased activity against α4β7 integrin; MLN-02, a humanized IgG1 monoclonal antibody to α4β7 integrin; and alicaforsen, an intercellular adhesion molecule-1 antisense oligodeoxynucleotide.

Authors of a review of the pivotal clinical trials for natalizumab in the treatment of multiple sclerosis and CD have noted that the drug has shown promising results in both diseases and appears to be superior to current therapies in reducing relapse rates. However, the authors also noted that 3 recent, confirmed case reports of PML have raised concern about the use of natalizumab in undefined patient subgroups or in combination with existing therapies. Because the drug was voluntarily taken off the market in March 2005 pending further evaluation of its safety, the authors pointed out that analysis of the drug's possible association with PML would determine the risk-benefit evaluation and the drug's eventual role as a therapeutic agent.

MLN-02, which inhibits leukocyte trafficking, has been evaluated in a dose-ranging induction study involving 185 patients with active CD. Patients in this study received IV doses of MLN-02 0.5 mg/kg and 2 mg/kg at weeks 0 and 4. Although response, the primary endpoint, was not achieved, the higher dose was found to be significantly better than the lower dose for clinical remission.

Similar to natalizumab and MLN-02, alicaforsen (also referred to as ISIS 2302) inhibits leukocyte trafficking. Thus far, it has been evaluated in patients with steroid-refractory CD, steroid-refractory chronic active CD, active CD, and steroid-dependent CD. A dosing-interval, placebo-controlled trial in 75 patients with steroid-refractory chronic active CD found that alicaforsen was not effective in inducing steroid-free remission at week 14, the primary endpoint. However, the study did find that a higher proportion of patients receiving alicaforsen achieved a steroid dose less than 10 mg/day at week 14 (48% vs 33% for placebo) and week 26 (55% vs 40% for placebo), in addition to a glucocorticoid dose of 0 mg at week 26 (23% vs 6.7% for placebo).

A more recent dose-ranging trial of high-dose alicaforsen in 22 patients with active CD found that fixed doses of 300 mg or 600 mg, but not 250 mg, administered IV 3 times a week for 4 weeks achieved the desired drug exposure and may be an effective therapy for CD. Five patients withdrew after 1 to 3 infusions because of infusion-related events, but 9 of the remaining 17 experienced clinical remission for a median duration of 14 weeks. The overall response, defined as a decrease of at least 70 points on the CDAI, was 41% at week 8 and 47% at week 12.
A double-blind, placebo-controlled trial involving 299 patients with steroid-dependent CD found that alicaforsen was not effective in inducing remission, but was associated with steroid sparing. At week 14, a higher proportion of patients receiving alicaforsen was successfully withdrawn from steroids (78% vs 64% for placebo). In addition, there were greater reductions in CDAI scores in treated patients at 14 weeks (136 points) than in those receiving placebo (52 points).

**Colony-Stimulating Factors**

Chronic granulomatous disease, glycogen storage disease, and Chediak-Higashi syndrome are characterized by neutrophil dysfunction and are associated with gut inflammation that is phenotypically similar to CD. Because patients with chronic granulomatous disease have been shown to respond to immune system stimulation with sargramostim, a recombinant granulocyte macrophage colony-stimulating factor, this agent was evaluated as a potential therapy in patients with CD.

As demonstrated in a randomized placebo-controlled trial in 124 patients with active CD, subcutaneous sargramostim 6 µg/kg/day for 8 weeks was not significantly different from placebo for clinical response (a decrease from baseline of at least 70 points in the CDAI score at the end of treatment), the primary endpoint. However, the drug was more effective than placebo in achieving secondary endpoints. Significantly more patients in the sargramostim group achieved a clinical response, defined by a decrease from baseline of at least 100 points in the CDAI score or a CDAI score of less than 150, and remission defined by a CDAI score of less than 150. Rates for both types of clinical response and remission were also higher in the sargramostim group compared to the placebo group on day 29 of treatment and 30 days after treatment. Sargramostim was also associated with significant improvements in quality of life.

The secondary endpoint findings suggest that sargramostim decreases disease severity and improves quality of life. However, the higher incidence of mild to moderate infusion-site reactions and bone pain in the patients receiving sargramostim, in addition to the occurrence in 3 patients of serious adverse events that were possibly or probably related to the drug, is a matter of concern.

Another immunostimulant, the granulocyte colony-stimulating factor filgrastim, was evaluated in a 12-week, open-label study of 20 patients with active CD. By week 12, 11 patients had a decrease in CDAI score of at least 70 points, and 5 achieved a sustained remission. Moreover, 3 of 4 patients with fistulas had a positive response. The most common adverse event was bone pain, which was usually mild and resolved with continued treatment.

**Other Novel Therapies**

Crohn’s disease is uncommon in less developed areas of the world where most of the population carries worms. Because helminths have been shown to diminish immune responsiveness in naturally colonized humans and reduce inflammation in experimental colitis, it has been theorized that exposure to helminths may play an important role in preventing or ameliorating CD.

Two open-label studies investigating the efficacy and safety of therapy with ova from the porcine whipworm Trichuris suis have found that this novel approach is a safe and effective alternative in patients with CD and UC. The findings also support the premise that natural exposure to helminths, such as T suis, protects against immunological disease, such as CD and UC, by down-regulating aberrant intestinal inflammation.

In one of the studies, 29 patients with active CD ingested 2500 live T suis ova every 3 weeks for 24 weeks and monitored for changes in the CDAI. At week 24, 23/29 patients responded with a decrease in CDAI of at least 100 points from baseline or a CDAI score of less than 150, and 21/29 patients achieved remission (CDAI <150). Similar findings with regard to response and remission were noted at week 12.

In the other study, 4 patients with active CD and 3 patients with UC were initially given a single oral dose of 2500 live T suis ova and followed every 2 weeks for 12 weeks. Usual doses of baseline medications were continued throughout the study, and patients were regularly monitored for changes in clinical status, laboratory values, and disease activity and quality-of-life indices. Maintenance treatment with repeated doses of 2500 live ova at 3-week intervals for 28 weeks was also assessed by the same evaluation parameters in 2 of the patients with CD and 2 with UC.

All patients improved clinically during the initial treatment and observation period without any adverse clinical events or laboratory abnormalities. Three of
the 4 patients with CD achieved remission, and the fourth experienced a clinical response without achieving remission. All 3 patients with UC experienced a reduction in disease activity, and 6 of 7 patients had improved quality-of-life scores. Although the beneficial effects of the initial dose were temporary, all 4 patients receiving multiple T suis doses for maintenance experienced sustained clinical improvement and no adverse effects.

OTHER THERAPIES

Growth hormone and thalidomide are other therapies that have been investigated for their applicability in the treatment of CD. Growth hormone has been shown to play an important role in modulating the distribution of visceral fat, which often accumulates in patients with CD.67 In a study of 20 men with CD who were not taking glucocorticoids and 20 normal controls who were matched for age, gender, and body mass index, mean serum levels of growth hormone, insulin-like growth factor-1, and testosterone were lower in men with CD than in controls. However, the percentage of body and intra-abdominal fat was significantly higher in the men with CD, and the ratio of intra-abdominal to total body fat was also higher in the men with CD. The percentage of intra-abdominal fat remained higher in patients with CD even after the investigators controlled for testosterone and mean serum levels of growth hormone, suggesting that growth hormone contributes independently to differences in the percentages of intra-abdominal fat and thus may have a role in CD therapy.

Findings from a preliminary study of growth hormone in 37 adults have suggested that it may be beneficial in patients with chronic active CD.68 Patients with moderate to severe active CD were randomly assigned to daily self-administered subcutaneous injections of growth hormone or placebo for 4 months and monitored for changes in CDAI scores. At 4 months, there was a significant decrease in CDAI scores in the group receiving growth hormone (143 ± 144 vs 19 ± 63 for placebo; P = .004). Side effects in those patients receiving growth hormone included edema (n = 10) and headache (n = 5), which resolved within the first month of treatment.

The investigators noted that they did not study whether growth hormone therapy would be beneficial if it were initiated at the onset of CD.68 However, they recommended further study in this area, in addition to a larger multicenter study to confirm their results and ascertain optimal dosage and duration and frequency of therapy needed to induce and maintain clinical remission.

Growth failure is a frequent complication in children with CD. The success of recombinant growth hormone in children with growth failure due to pituitary insufficiency or various other conditions prompted a 2-phase pilot study in 7 children with CD and short stature.69 In the first phase, the children were randomized to growth hormone 0.05 mg/kg/day or placebo for 1 year. In the second phase, children who received placebo in the first year were switched to growth hormone for various time periods. All children were followed every 4 months for up to 2 years.

At the dose given, growth hormone did not stimulate catch-up growth.69 Observed changes in growth within and for each of the study phases were not significantly different. Moreover, only 2 of the children later reached expected adult height. However, the finding that 2 of the children grew only when nutritional supplementation was added raises the possibility that growth hormone plus nutritional supplementation might be beneficial in promoting sustained catch-up growth and should be investigated.

Thalidomide, which decreases the production of TNF-α, has been studied in a small number of patients with CD. It serves as an example of a potentially new and novel use of an old agent. In 1 open-label pilot study involving 12 adult males with chronic active steroid-dependent CD, low-dose thalidomide (50 mg every night in 6 patients, or 100 mg every night in the remaining 6) was well tolerated and effective over a 12-week period.70 Steroid doses remained stable during the first 4 weeks of the study, then tapered during weeks 5 to 12.

Disease activity scores decreased consistently in all patients during the first 4 weeks, with a response rate of 58% and a remission rate of 17%.70 Clinical remission was generally maintained, despite steroid tapering, and 44% of the patients were able to discontinue steroids entirely. Response and remission rates during weeks 5 to 12 were 70% and 20%, respectively. Side effects, including drowsiness, peripheral neuropathy, edema, and dermatitis, were generally mild and transient.

Given these findings, the investigators noted that controlled multicenter trials of thalidomide for CD...
were warranted. However, the demonstrated teratogenicity of thalidomide excludes it as a therapeutic option for women who are capable of bearing children.

Another open-label study involving 16 men and 6 women with refractory CD and/or draining fistulas found that higher doses of thalidomide were effective in some of these patients. Thalidomide 200 mg or 300 mg every night at bedtime was administered to 18 and 4 patients, respectively, for 12 weeks, and CDAI and goal interval scores were assessed at weeks 0, 4, and 12. Of the 16 patients who completed 4 weeks of treatment, 12 had a clinical response and 4 achieved clinical remission. All 14 patients who completed 12 weeks of treatment met the criteria for clinical response and 9 (3 with luminal disease, 6 with fistulas) achieved clinical remission.

Given the highly restricted ability to prescribe thalidomide, its potent teratogenicity, and its association with severe and potentially irreversible peripheral neuropathy, it is unlikely that this drug will be widely used in the treatment of CD. However, second-generation agents with potentially less toxicity are being investigated.

CONCLUSIONS

Conventional drug therapies, such as aminosalicylates, corticosteroids, immunomodulators, and antibiotics, are used as initial therapy with or without anti-TNF agents in most patients with CD. However, they are associated with several important limitations that underscore the need for newer agents to provide what the conventional drugs lack.

For example, corticosteroids provide rapid relief of inflammatory symptoms and are effective in inducing remission, but they do not modify disease, nor are they effective in maintaining remission. Moreover, they are associated with resistance, dependence, and numerous short- and long-term side effects in a substantial number of patients.

In contrast, the immunomodulators work slowly, and are therefore effective in maintaining remission and modifying disease. However, although AZA/6-MP have long been available and widely used in CD, data on the use of methotrexate and cyclosporine in CD are sparse and additional clinical trials are clearly needed.

The approval of infliximab, the first TNF antagonist, in 1998 for induction of remission marked the beginning of a new era in CD therapy. This agent class targets TNF, the major pro-inflammatory cytokine involved in CD, and modifies disease. Infliximab, which is also approved for maintaining remission in CD and the treatment of rheumatoid arthritis, has also been shown to be effective in healing fistulas and reducing corticosteroid requirements.

Adalimumab is approved for the treatment of rheumatoid arthritis and phase III trials evaluating the drug for maintenance of remission in CD are under way. Preliminary studies have found that another TNF antagonist, certolizumab pegol, is also effective in inducing and maintaining remission.

Several other therapies targeting other components of the inflammatory cascade and the immune system that are involved in CD are under active investigation. These include IL-6 and IL-12 antagonists, anti-IFN-γ antibodies, anticellular adhesion molecule antibodies, and colony-stimulating factors.

It is hoped that continued study of TNF antagonists, investigational agents, and conventional therapies will ultimately identify appropriate dosing schedules and the best sequence of drugs to optimize response and remission rates, minimize adverse events, and promote complete healing of the mucosa in patients with CD.

REFERENCES


