

Advances in the Treatment of Crohn's Disease

LAURENCE J. EGAN and WILLIAM J. SANDBORN

Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota

The medical therapy of Crohn's disease has improved considerably in recent years. In large part, this is due to the introduction of new efficacious agents, both "biologics" and traditional small molecules. Further study of older drugs has also advanced our ability to devise the optimum approach to individual Crohn's disease patients by better clarifying the benefits, adverse effects, and means to optimize doses of established medications. In this review, we present an evidence-based approach to the medical management of active Crohn's disease, Crohn's disease in remission, and perianal Crohn's disease that emphasizes recent advances that have come from the results of randomized controlled clinical trials.

In recent years, a remarkable number of controlled clinical trials in Crohn's disease have been completed. Many of these trials have evaluated the efficacy of members of the new class of "biologic" agents, principally monoclonal antibodies against cell surface-expressed molecules that have proven pathogenic roles in Crohn's disease but not necessarily ulcerative colitis (Table 1). In some of these trials, the biologic agents performed better than placebo, and, without doubt, these results constitute the major advances in the medical therapy of Crohn's disease in the past 5 years. Meta-analysis has also been utilized recently to evaluate carefully the usefulness of older drugs in Crohn's disease therapy when multiple trials existed. These analyses, together with the findings of trials of the newer anti-Crohn's disease drugs, are allowing the definition of a modern evidence-based approach to the rational medical management of Crohn's disease that differs significantly from the traditional approach of stepwise introduction of drugs of greater activity. A comparison of the efficacious agents previously and currently available for use in luminal Crohn's disease is shown in Figure 1 and for use in fistulizing Crohn's disease is shown in Figure 2.

In this review, we provide an evidence-based approach to the optimum current medical management of active Crohn's disease, Crohn's disease in remission, and perianal Crohn's disease, emphasizing the results of recent randomized clinical trials of traditional drugs and biologic agents. Adoption of this evidence-based approach

will, at a minimum, decrease the futile use of ineffective agents and offers the promise of significantly improving patient outcomes and the possibility of altering the natural history of Crohn's disease. Because many Crohn's disease therapies have been associated with potentially serious adverse events, suggested procedures for monitoring for specific drug toxicities are presented in Table 2.

Active Inflammatory Crohn's Disease

The results of randomized controlled clinical trials performed in the 1980s and 1990s laid the foundation for the current optimum approach to managing mild to moderately active Crohn's disease. Corticosteroids, both prednisone (or equivalent doses of other conventional steroids such as prednisolone) and controlled ileal release budesonide were found to be consistently superior to placebo, sulfasalazine, or mesalamine for the induction of remission in mild to moderately active ileal or ileocolonic Crohn's disease.¹⁻⁶ One notable exception was a trial of budesonide in North American patients, which showed improved responses compared with placebo during active disease but no efficacy over placebo for remission induction.⁷ Because of significantly less adrenal suppression and other glucocorticoid side effects, controlled ileal release budesonide is preferable to conventional corticosteroids such as prednisone in patients with ileal and right colon disease. Sulfasalazine was previously established to be significantly superior to placebo for left colon disease.^{1,2} No other medications have consistently been shown to be superior to placebo or to other less effective controls for induction of remission in mild to moderately active Crohn's disease. Infliximab (see below), which is usually reserved for patients with more active disease, is also an effective remission induction therapy for moderately active Crohn's disease.⁸

A number of recent studies have examined the effects of combination therapy with corticosteroids and antibi-

Table 1. Biologic Agents Evaluated for Use in Crohn's Disease in Randomized, Double-Blind, Placebo-Controlled Trials

Agent	Class	Target	Efficacy	Stage of development
Infliximab (Remicade)	Chimeric mouse/human IgG1 monoclonal antibody	TNF- α	Active disease, fistulizing disease, remission maintenance	Approved
Etanercept (Enbrel)	Human TNFR1 fusion protein	TNF- α	No	Approved for rheumatoid arthritis
CDP571	Humanized IgG4 monoclonal antibody	TNF- α	Active disease high CRP subgroup only	Not approved
CDP870	Pegylated humanized antibody fragment	TNF- α	Active disease high CRP subgroup only	Not approved
Natalizumab (Antegren)	Humanized IgG4 monoclonal antibody	α_4 integrins	Active disease	Not approved

TNF- α , tumor necrosis factor α ; CRP, C-reactive protein.

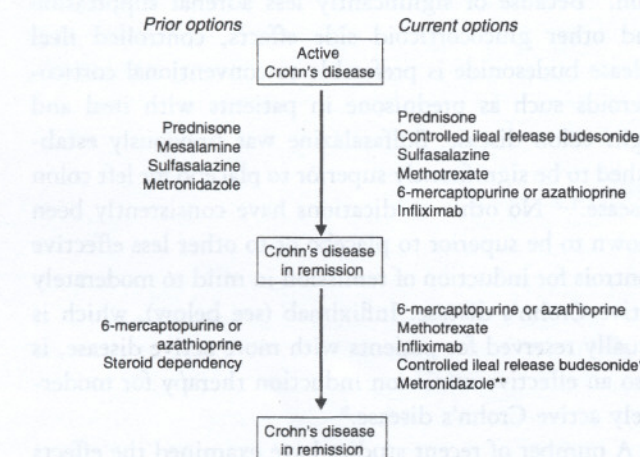
otics in active Crohn's disease. The addition of ciprofloxacin and metronidazole to budesonide was not superior to budesonide monotherapy.⁹ Similarly, the addition of ciprofloxacin to prednisolone therapy does not produce any additional clinical benefit.¹⁰

Corticosteroids are quite successful for the induction of remission in many Crohn's disease patients with active inflammatory disease. However, some patients experience adverse effects of these drugs (steroid intolerant patients), experience little or no improvement in disease activity (steroid-resistant patients), or experience a flare in disease activity during or after corticosteroid dose reduction (steroid-dependent patients). These patients who fail to respond to first-line therapy and patients with more severe symptoms are usually considered as having moderate to severe Crohn's disease, and, prior to the introduction of biologic agents in the late 1990s, such patients had few nonsurgical options. Infliximab is a chimeric mouse/human monoclonal antibody against tu-

mor necrosis factor (TNF)- α . In the pivotal trial of infliximab, administered as a single infusion of 5 mg/kg for active Crohn's disease, 33% of patients entered remission, a significant benefit over the placebo remission rate of 4%, and 81% of patients treated with infliximab improved compared with 17% of controls.⁸ The AC-CENT I trial¹¹ found that 58% of 573 patients responded to an initial infusion of infliximab 5 mg/kg. Although there was no placebo arm at this phase of this study, these observations nevertheless further support the use of this agent in Crohn's disease patients who do not fully respond to corticosteroids and who do not require surgery.

A number of other anti-TNF- α agents have been evaluated for active Crohn's disease. CDP571 is a humanized mouse monoclonal antibody against TNF- α , and CDP870 is a pegylated fragment of an anti-TNF- α antibody. In large clinical trials involving hundreds of patients, these agents demonstrated induction of short-term (weeks 2–4) response but were not significantly better than placebo for maintenance of clinical response beyond 4 weeks.^{12,13} However, when the subgroup of patients with elevated C-reactive protein was evaluated, highly significant and longer-term benefit was observed for both CDP571 and CDP870.¹⁴ Thus, elevated C-reactive protein may be a predictor of favorable responses to anti-TNF- α therapies.

Natalizumab is a humanized mouse monoclonal antibody against α_4 integrin that blocks the efflux of activated lymphocytes and monocytes from the vasculature into tissues. Three placebo-controlled trials of natalizumab have been performed in active Crohn's disease. A very small pilot study and a phase II dose-ranging study suggested significant efficacy compared with placebo.^{15,16} However, in the pivotal phase III trial, natalizumab 300 mg every 4 weeks was not superior to placebo for clinical improvement at the primary study end point of 10 weeks.¹⁷ Interestingly, similar to the subgroup observa-



* prolongs time to relapse but does not maintain remission at 1 year
 ** maintains endoscopic but not symptomatic remission

Figure 1. Comparison of the previously and currently available agents that are efficacious for the treatment of active luminal Crohn's disease and Crohn's disease in remission.

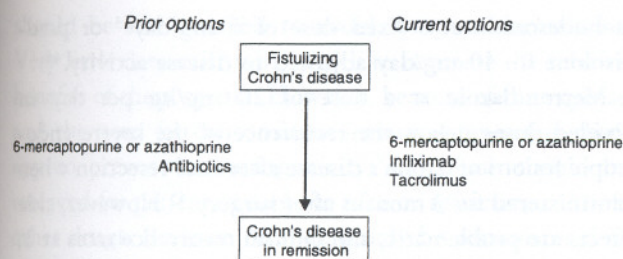


Figure 2. Comparison of the previously and currently available agents that are efficacious for the treatment of fistulizing Crohn's disease.

tions in the CDP571 and CDP870 trials, subjects with elevated C-reactive protein had a statistically and clinically significant response to natalizumab. This suggests that elevated C-reactive protein may be a biomarker of potentially reversible inflammation or, alternatively, a biomarker of lower rate of placebo response.

Small case series had reported beneficial responses to methotrexate in inflammatory bowel disease patients refractory to or intolerant of standard therapies. These observations were carefully studied in patients with inflammatory Crohn's disease who did not respond fully to prednisone.¹⁸ Weekly intramuscular injections of 25 mg methotrexate induced remission in about 40% of patients, twice the placebo rate. Improvement is seen typically after about 4–6 weeks of therapy.

It was previously established that 6-mercaptopurine or azathioprine were beneficial in patients with active Crohn's disease who failed other therapies,^{19,20} with the best results observed in patients when these slow-acting drugs were initially administered with a corticosteroid.¹⁹ An 18-month trial evaluated 6-mercaptopurine, in combination with a tapering schedule of prednisone, as initial therapy for children with moderate to severely active Crohn's disease.²¹ Although early induction of remission was similar in both groups (89%), children randomized to receive 6-mercaptopurine required less prednisone to remain in remission and experienced significantly longer periods of remission than did those in the placebo group. The results of this trial strongly suggest that introduc-

tion of 6-mercaptopurine early in the course of Crohn's disease may produce superior clinical outcomes. However, additional data regarding the safety of these agents introduced at diagnosis in a larger number of patients are needed.

Based on these data, an evidence-based approach to the management of Crohn's disease patients with less than complete response to standard doses of conventional corticosteroids, controlled ileal release budesonide, or sulfasalazine calls for the addition of oral 6-mercaptopurine 1.5 mg/kg per day or azathioprine 2.0–2.5 mg/kg per day, injections (subcutaneous or intramuscular) of methotrexate 25 mg once per week, or infliximab 5 mg/kg. Although head-to-head comparisons have not been made, the time to response appears to be fastest with infliximab (1–2 weeks), intermediate with methotrexate (4–6 weeks), and slowest with 6-mercaptopurine or azathioprine (4–8 weeks). However, because infliximab is more expensive and is immunogenic, it is our practice to begin with 6-mercaptopurine, azathioprine, or methotrexate, usually in conjunction with corticosteroids, which produce a more rapid benefit. Those patients who fail to improve consistently on these medications should be treated with infliximab. In these patients, azathioprine, 6-mercaptopurine, or methotrexate are continued to minimize the immunogenicity of infliximab.²² The optimum induction regime of infliximab for active Crohn's disease appears to be 3 infusions at 0, 2, and 6 weeks because this decreases immunogenicity and gives a slight increase in efficacy over a single dose.²³

Crohn's Disease in Remission

With the treatment approach outlined above, most patients with active inflammatory Crohn's disease who do not require an operation should enter a symptomatic remission. Those who fail to respond to medical therapy can usually be operated on and enter surgically induced remission. The major challenge in the care of this chronic illness thus lies in keeping the Crohn's

Table 2. Toxicity Monitoring in Crohn's Disease Therapy

	Pretherapy	During therapy	Toxicity warranting discontinuation
Azathioprine or 6-mercaptopurine	Thiopurine methyltransferase, hepatic aminotransferases, blood count	Blood count and hepatic aminotransferases, initially weekly then every month; consider 6-methylmercaptopurine	Pancreatitis, rash, opportunistic infection, lymphoma
Methotrexate	Blood count, hepatic aminotransferases (liver ultrasound and biopsy if elevated)	Blood count and hepatic aminotransferases, initially weekly then every month; liver biopsy controversial	Hepatotoxicity, pneumonitis, opportunistic infection
Infliximab	Tuberculosis skin test, chest X-ray	None	Opportunistic infection, severe infusion reaction

disease patient symptom free and able to lead a full and productive life unencumbered by recurrent episodes of disease activity or the adverse effects of medications.

6-Mercaptopurine and azathioprine are the benchmark drugs for the maintenance of long-term symptomatic remission in Crohn's disease. Although the benefit of these drugs is well established,^{19–21,24} a recent noninferiority (equivalence) study addressed the question of when to discontinue 6-mercaptopurine or azathioprine in patients who experience years-long remission. Among Crohn's disease patients in remission for at least 42 months, withdrawal of azathioprine leads to an 18-month relapse rate of 21% compared with 8% among the group randomized to continue active treatment, with statistical analysis indicating that azathioprine withdrawal was not equivalent to continued azathioprine.²⁵ Thus, both in induction followed by long-term treatment studies and in a withdrawal of treatment trial, azathioprine and 6-mercaptopurine have been found to be superior to placebo for maintenance of remission in Crohn's disease. Despite these observations, 6-mercaptopurine and azathioprine are not universally effective, require regular toxicity monitoring, and have significant adverse event profiles. For this reason, safer and more effective remission-maintaining drugs have been sought.

5-Aminosalicylic acid drugs have been extensively studied for the prevention of Crohn's disease flares. The results of some of these studies suggested that mesalamine was efficacious for the maintenance of medically or surgically induced remission in Crohn's disease,^{26–28} but more studies showed no benefit over placebo.^{29–35} Meta-analysis showed no significant benefit over placebo in medically induced remission or a marginal benefit in surgically induced remission. Similarly, sulfasalazine^{1,2,36} and olsalazine³⁷ were found to be not superior to placebo for remission maintenance. For these reasons, 5-aminosalicylic acid drugs should not be prescribed to Crohn's disease patients for maintenance of remission.

Conventional corticosteroids are not effective for maintaining Crohn's disease remission at doses low enough to avoid obvious adverse effects with long-term use. However, controlled ileal release budesonide 6 mg/day was found to be effective for prolongation of time to relapse and maintenance of remission at 6 months but not 1 year in patients with Crohn's disease in medically induced remission.^{38–40} Budesonide 6 mg/day is more effective than placebo or mesalamine 3 g/day for maintenance of remission in patients with steroid-dependent Crohn's disease.^{41,42} Maintenance therapy with a variable dose of budesonide 0–9 mg/day to maintain symptomatic remission results in similar control of disease activity

as budesonide at a fixed dose of 6 mg/day⁴³ or prednisolone 0–40 mg/day adjusted to disease activity.⁴⁴

Metronidazole at a dose of 20 mg/kg per day in divided doses delays the recurrence of the severe endoscopic lesions of Crohn's disease after ileal resection when administered for 3 months after surgery.⁴⁵ However, side effects are problematic, and clinical recurrence rates at 1, 2, and 3 years in the intention-to-treat population were not significantly lowered by 3 months of metronidazole therapy. Thus, the role of metronidazole for postoperative maintenance of remission in clinical practice remains uncertain.

Methotrexate maintenance therapy was studied in patients who had entered symptomatic remission with methotrexate 25 mg once weekly.⁴⁶ At a dose of 15-mg weekly, methotrexate was superior to placebo in this 40-week trial, with long-term remission rates of 65% vs. 39% in placebo-treated patients. Furthermore, 55% of patients who relapsed and were retreated with methotrexate 25 mg/wk entered symptomatic remission at 40 weeks. It is unknown whether methotrexate maintenance therapy is effective in Crohn's disease patients who enter remission with another drug or with surgery.

The benefit of 8 weekly infusions of infliximab in Crohn's disease patients who experienced clinical benefit from a single infusion of this agent was studied in a large clinical trial involving 573 patients. The ACCENT I trial reported that, of 58% patients who responded to an initial infusion of infliximab 5 mg/kg, remission rates after 30 weeks were 21%, 39%, and 45% in the groups randomized to 8 weekly maintenance treatments with placebo, 5 mg/kg or 10 mg/kg infliximab, respectively.¹¹ Thus, about 25% of patients who enter into a long-term treatment program with 8 weekly infliximab infusions should remain in long-term remission. Dose escalation from 5 mg/kg to 10 mg/kg or dose interval shortening from every 8 weeks to every 6 weeks or even every 4 weeks appears to increase the number of patients successfully maintained.

These data, along with the results of older studies, support the following management approach for the treatment of Crohn's disease in remission. Azathioprine or 6-mercaptopurine, methotrexate, and infliximab have been proven efficacious for maintaining medically induced remission in Crohn's disease. Although budesonide prolongs the time to relapse, it does not meet the conventional definition of efficacy (maintenance of remission for 1 year). Most patients who enter remission with drug therapy will relapse without maintenance treatment. Therefore, azathioprine, 6-mercaptopurine, methotrexate, or infliximab, and, in some cases budesonide,

should be administered to avoid symptomatic relapse. Very little data exist with which to compare the relative benefits of these agents. However, because of the expense and the need for concomitant immunosuppressive therapy to prevent immunogenicity, infliximab should be reserved for patients unable to take or refractory to these other drugs. Budesonide should only be administered to patients with distal small intestine and right colon disease, and most studies suggest that the duration of benefit with maintenance budesonide is less than 1 year. This is considerably shorter than the benefit reported in the studies of azathioprine, 6-mercaptopurine, and methotrexate for remission maintenance. Therefore, azathioprine, 6-mercaptopurine, or methotrexate should be prescribed for most Crohn's disease patients in medically induced remission. Symptomatic relapse tends to occur after azathioprine or 6-mercaptopurine are stopped, so therapy with these agents should be continued indefinitely in most patients in the absence of a contraindication to continuation. Patients who require infliximab to enter remission, but relapse despite the use of azathioprine, 6-mercaptopurine or methotrexate, should receive 8 weekly infusions of infliximab. Whether all patients require the immediate institution of maintenance therapy with one of these agents is unclear. Given the toxicity profile of the immunosuppressive agents and of infliximab, it may be reasonable to have 1 trial of no maintenance therapy (or continuation of budesonide at 6 mg/day following 9 mg/day induction) in patients with mild disease who are completing induction therapy.⁴⁷ However, data indicate that 56%–68% of Crohn's patients who are treated with corticosteroids are not in remission 1 year later,^{48,49} so most patients will require maintenance therapy, and practitioners should have a very low threshold for beginning immunosuppressive maintenance therapy.

The time to symptomatic relapse after intestinal resection in Crohn's disease is highly variable. Because many patients with a short segment of stricturing Crohn's disease at the terminal ileum do not experience recurrent symptoms soon after surgery, we do not necessarily treat all postoperative patients. Natural history studies have shown that symptomatic recurrence is preceded by endoscopic recurrence and that the severity of endoscopic changes predicts future disease activity.^{50,51} Therefore, an alternative to treating all patients with azathioprine or 6-mercaptopurine is to stratify postoperative patients by the presence or absence of neoterminal ulcers 6–12 months after surgery and to treat only those with severe ulcers. However, immediate postoperative maintenance therapy may be indicated in those patients

with residual unresected disease, a prior history of aggressive disease (including internal fistula or abscess), a short clinical course before surgery, or multiple prior resections. Metronidazole has been shown to reduce the frequency of severe ulcers after terminal ileum and right colon resection, but the utility of this agent in the prevention of symptomatic relapse has not been established.⁴⁵ Although postoperative remission maintenance studies are mostly lacking, we frequently prescribe azathioprine or 6-mercaptopurine in this patient population.

Perianal Crohn's Disease

Medical therapy of Crohn's disease causing perianal fistula and/or abscess requires thorough anatomic definition of the site of fistula tract(s), exclusion of abscess, and evaluation for the presence of inflammation of the rectal mucosa. This usually entails endoscopy and, frequently, a combination of endorectal ultrasound or magnetic resonance imaging of the pelvis and/or examination under anesthesia with appropriate surgical treatment of abscess cavities and fistula tracts.^{52–54} Rectal Crohn's disease should be treated as outlined above. Traditionally, antibiotics such as metronidazole are used for perianal fistulas, although no controlled evidence supports this practice. Infliximab 5 mg/kg administered at weeks 0, 2, and 6 and azathioprine 2–2.5 mg/kg or 6-mercaptopurine 1.5 mg/kg are the drugs with the best established roles for the medical treatment of active fistulizing disease.^{20,55} A recent placebo-controlled trial evaluated tacrolimus for the treatment of perianal Crohn's disease.⁵⁶ Although rates of complete fistula closure were not better in the active treatment group, more fistulas improved with tacrolimus than with placebo. Thus, in patients with active perianal fistula who do not respond to infliximab along with azathioprine or 6-mercaptopurine, tacrolimus is a potential alternative therapy.

The value of continued infliximab infusions in patients with fistula who had an initial response to 3 doses of infliximab 5 mg/kg was evaluated in the ACCENT II trial.⁵⁷ Sixty-nine percent of patients responded to the initial induction course of infliximab (defined as >50% reduction in number of draining fistulas) and were then randomized to maintenance infliximab every 8 weeks or placebo. The median time to loss of response was 14 weeks in placebo-treated patients vs. >40 weeks in infliximab-treated patients, a highly significant difference. Therefore, Crohn's disease patients with persistent or recurrent perianal fistula after an initial response to 3-dose infliximab induction therapy along with azathio-

prine or 6-mercaptopurine should be treated with 8 weekly infliximab infusions.

Conclusions

Physicians caring for Crohn's disease patients today have a greater array of therapeutic options to choose from than ever before, and this arsenal of agents is likely to expand if the promising results coming from early phase studies of both biologic and small molecule therapeutics are confirmed in pivotal phase III trials. These advances will translate into superior patient outcomes. With increasing complexity in the therapeutic decision making for Crohn's disease patients comes the need to identify subgroups of patients defined by the likelihood of response or toxicity from a particular agent. In this regard, the study of genetic predictors of responses to drugs has the greatest potential to permit the individualization of drug choice.⁵⁸ Thus, the next wave of advances in Crohn's disease therapy may come through the field of pharmacogenomics.

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Address requests for reprints to: Laurence J. Egan, M.D., Mayo Clinic, 200 First Street S.W., Rochester, Minnesota 55905. e-mail: egan.laurence@mayo.edu; fax: (507) 255-6318.

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