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# Ulcerative colitis: Responding to the challenges

## ABSTRACT

Aminosalicylates are the first-line therapy for patients with mild to moderate active ulcerative colitis. Treatment should start at dosages of 4.8 g per day of the active 5-aminosalicylate moiety, rather than starting at a lower dosage and increasing if treatment fails. Infliximab has been shown to be effective and is now approved by the US Food and Drug Administration for the treatment of moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy.

**A** 19-YEAR-OLD MAN PRESENTS to his primary care physician with a 3-month history of progressive diarrhea. He has abdominal cramping and four to six watery bowel movements daily, and he recently developed rectal bleeding. He has had no weight loss or fever and reports no recent travel, antibiotics, or risk factors for human immunodeficiency virus.

**Physical examination.** Vital signs are normal. He has mild abdominal tenderness in the left lower quadrant. On digital rectal examination, some blood is evident, but no other abnormalities are noted.

**Laboratory tests.** The hematocrit level is 35% (normal 41–50), thus indicating mild anemia. Stool studies detect no infectious agents.

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Colonoscopy reveals active colitis with erythema and loss of the normal vascular pattern, starting in the rectum and extending to the mid-transverse colon. Biopsy specimens show chronic active colitis. The findings are consistent with the diagnosis of ulcerative colitis.

Based on these findings, how should we treat this patient with newly diagnosed ulcerative colitis to induce remission? Will long-term therapy be required to maintain remission?

## DEFINING THE EXTENT AND THE SEVERITY

Ulcerative colitis, a form of inflammatory bowel disease, is defined as a chronic inflammatory condition involving the mucosa of the colon. The inflammation always starts in the rectum and progresses up the bowel to a varying extent in a continuous fashion. Alternating periods of flare-ups and remissions are typical.

To guide management, we must first determine the extent of the disease according to the following definitions:

- Proctitis: confined to the rectum
- Left-sided colitis: extends to the splenic flexure
- Extensive colitis: extends beyond the splenic flexure.

Based on the presentation and the results of the evaluation so far, our patient has extensive ulcerative colitis.

Clinical severity is graded as mild, moderate, severe, or fulminant, depending on the number of bowel movements per day and the presence of fever, tachycardia, and anemia (TABLE 1).<sup>1</sup> Our patient has active mild to moderate disease.

**How should we treat this patient with newly diagnosed ulcerative colitis?**

TABLE 1

**Grading the severity of ulcerative colitis**

GRADE	CHARACTERISTICS
<b>Mild</b>	Fewer than four bowel movements a day, with or without blood Normal erythrocyte sedimentation rate No signs of toxicity
<b>Moderate</b>	Four or more bowel movements a day Minimal signs of toxicity
<b>Severe</b>	More than six bloody stools a day and fever, tachycardia, anemia, elevated erythrocyte sedimentation rate
<b>Fulminant</b>	More than 10 stools a day, continuous bleeding, toxicity, abdominal tenderness or distention; requires transfusion; radiography reveals colonic dilation

ADAPTED FROM THE AMERICAN COLLEGE OF GASTROENTEROLOGY PRACTICE GUIDELINES FOR THE TREATMENT OF ULCERATIVE COLITIS IN ADULTS

**Oral steroids are generally not first-line therapy for mild to moderate disease**

### ■ TREAT MODERATE DISEASE WITH HIGH-DOSAGE AMINOSALICYLATES

According to the guidelines from the American College of Gastroenterology,<sup>1</sup> active, mild, or moderate extensive ulcerative colitis should be treated with sulfasalazine or another aminosaliclylate in dosages up to 4.8 g per day of the active 5-aminosalicylic acid (5-ASA) moiety. Oral steroids are generally not recommended as first-line therapy for patients with mild to moderate disease.

Many good aminosaliclylate agents are available, sulfasalazine being the oldest. All the aminosaliclylates are comparable in terms of efficacy. These agents work topically in the colon rather than systemically. Several have a diazo bond that is cleaved by colonic bacteria, releasing 5-ASA and exerting a topical effect in the colon. Mesalamine (Asacol) is coated and releases 5-ASA at a pH of 7 or greater, which is the pH of the terminal colon.

### Experts and evidence support starting with a high dosage

The agents differ in the dosages approved by the US Food and Drug Administration (FDA). In practice, many clinicians start with low dosages and escalate to higher dosages if

needed. However, experts recommend starting with a high dosage.

A Double-Blind, Randomized, 6-Week, Parallel-Group Design Clinical Trial to Assess the Safety and Efficacy of Asacol 4.8 g/Day Versus Asacol 2.4 g/Day for the Treatment of Moderately Active Ulcerative Colitis, or ASCEND II,<sup>2</sup> was a multicenter, double-blind trial in the United States and Canada that included 386 patients with mild to moderate ulcerative colitis who received mesalamine either at the FDA-approved dosage of 2.4 g/day (six 400-mg tablets) or at a dosage of 4.8 g/day (six 800-mg tablets, which are not yet available). Both regimens induced response and remission, but the higher dosage was significantly more effective than the standard dosage at week 6 (71.8% vs 59.2%, respectively,  $P = .036$ ). Relief from symptoms was also more rapid in patients taking the higher dosage: rectal bleeding stopped at a median of 9 days vs 16 days with the standard dosage ( $P = .035$ ).

The higher dosage was more effective in all categories of extent of disease (proctitis, proctosigmoiditis, left-sided colitis, and pancolitis), but these differences were not statistically significant.

This study confirms that higher dosages of 5-ASA lead to an improved response in patients with moderately active ulcerative colitis compared with standard dosages.

The new 800-mg tablet, if approved, will cut the number of tablets needed from 12 per day to 6 per day and should help patients to better adhere to therapy. Kane et al<sup>3</sup> found that only 40% of patients with quiescent ulcerative colitis adhered to maintenance therapy, with adherence defined as taking at least 80% of prescribed medications. Patients who were not adherent were five times more likely to develop a clinical relapse than those who were adherent.<sup>4</sup> Forgetfulness, the inconvenience of so many pills, and feeling well were cited as reasons for not adhering to maintenance therapy.

### ■ REMISSION, THEN RELAPSE OF ULCERATIVE COLITIS

Our patient is treated with mesalamine 4.8 g per day (12 pills, 400 mg each) and he enters

TABLE 2

## Do immunomodulators induce remission of inflammatory bowel disease? What the available data say

AGENT	EFFECTIVE IN ULCERATIVE COLITIS?	EFFECTIVE IN CROHN DISEASE?
6-Mercaptopurine (Purinethol), azathioprine (Imuran)	Possibly	Yes
Methotrexate	No	Yes
Cyclosporine (Neoral)	Yes	Possibly
Infliximab (Remicade)	Yes	Yes

clinical remission. Over the next 6 months, he becomes less adherent to his drug regimen. His disease flares up again and is now more severe than before. Despite being prescribed mesalamine 6 g per day and two courses of corticosteroids, his condition responds only partially.

He returns to the clinic and reports having 8 to 10 bowel movements per day, bleeding with most bowel movements, and abdominal cramping. The white blood cell count is elevated (on prednisone therapy) at  $15.2 \times 10^9$  cells/mL, and the hematocrit level is 31%.

Repeat flexible sigmoidoscopy shows moderately active colitis. Biopsy shows no evidence of cytomegalovirus infection. Stool cultures and *Clostridium difficile* assay are negative.

### ■ IMMUNOMODULATORS FOR SEVERE DISEASE

The next step in the medical management is to consider immunomodulators. Good data exist for the efficacy of immunomodulators and anti-tumor necrosis factor agents for treating Crohn disease, but not as much data are available for ulcerative colitis (TABLE 2).

Until recently, an important unanswered question was whether we should use infliximab (Remicade) for ulcerative colitis. In 1998, the FDA approved infliximab for treating Crohn disease. Over the next 6 years, only limited information existed about its use for ulcerative colitis: a few case series suggested benefit, one randomized clinical trial was started then stopped due to slow enrollment, a small randomized clinical trial showed no

benefit, and anecdotal experiences varied about its efficacy.

In late 2005, two randomized clinical trials were published that evaluated infliximab for inducing and maintaining remission in patients with ulcerative colitis. The Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2, respectively)<sup>5</sup> involved 728 patients at 117 sites, making this the largest group of patients with ulcerative colitis studied in a treatment trial. The patients had active moderate to severe disease, and they either were concurrently being treated with standard therapy or had been unsuccessfully treated or unable to tolerate standard therapy in the past.

Patients in both studies were randomized to treatment with infliximab (5 or 10 mg/kg) or placebo intravenously, using a three-dose induction regimen at 0, 2, and 6 weeks. Patients were assessed for induction of remission at week 8, then received repeat doses every 8 weeks for 30 weeks in the ACT 2 trial and for 54 weeks in the ACT 1 trial.

In both studies at week 8, infliximab at each of the two dosages was statistically superior to placebo for inducing both clinical response and clinical remission. At weeks 30 and 54, a small drop-off was seen in the number of people who continued to respond, but both infliximab dosages remained statistically better than placebo for maintaining both clinical response and clinical remission. For the even stricter definition of “remission and off corticosteroids by week 54,” the 5-mg/kg dose was statistically superior to placebo and the 10-mg/kg dose offered a numerical but not a statistically significant advantage.

**Infliximab can induce and maintain remission in moderate-severe ulcerative colitis**

**Adverse effects similar to those of previous studies**

In ACT 1, 32% of patients taking 5 mg/kg and 35% of those taking 10 mg/kg developed an infection requiring antimicrobial therapy (including one case of tuberculosis in a patient taking the higher dosage) vs 21% of patients in the placebo group ( $P = .01$ ). In ACT 2, no differences in the rate of serious infections were found between the two groups.<sup>5</sup>

Another concern is whether infliximab increases the risk of cancer. An elderly man who was receiving infliximab 5 mg/kg and who had an elevated prostate-specific antigen level at baseline developed prostatic adeno-

carcinoma. Another patient who received the 5-mg/kg dose developed colon cancer. One patient in the placebo group developed a basal cell skin cancer.

In ACT 1 and ACT 2, patients taking infliximab were more likely to develop anti-nuclear and anti-double-stranded DNA antibodies than patients taking placebo, but only one patient in the infliximab group developed a lupus-like syndrome.

These trials showed that infliximab helps to both induce and maintain remission in patients with moderate to severe active ulcerative colitis. The side-effect profile is similar to what we expect from previous studies of Crohn disease. ■

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