

American Gastroenterological Association Institute Technical Review on Corticosteroids, Immunomodulators, and Infliximab in Inflammatory Bowel Disease

See CME Quiz on page 932.

The disorders collectively known as inflammatory bowel disease (IBD) include Crohn's disease (CD) and ulcerative colitis (UC). CD, initially credited as having been described in 1932 by Drs Burrill Crohn, Gordon Oppenheimer, and Leon Ginzburg,¹ is an idiopathic transmural chronic inflammatory disorder affecting the gastrointestinal tract. UC, on the other hand, is credited to have been described by Drs Wilks and Moxon in 1875.²

These disorders spare no socioeconomic class, age, sex, or country of origin. These disorders are relatively common in the United States, accounting for disease in approximately 1 million individuals, with similar numbers in Europe. These complex disorders may have varied presentations and complications that ensue during their course, as has been evidenced by wide variations in clinical practice. This position statement reviews the evidence-based medicine and current practice patterns for the treatment of IBD in adults with 3 classes of drugs: corticosteroids, immunomodulators, and infliximab. The intent of this position statement is to bring consistency to patient care, but this should not necessarily be viewed as the standard of care for all patients. Individual care of patients should be managed on the basis of all clinical data available for that particular case. Patient preferences should be sought in an effort to make decisions in a partnership between patients and health care professionals.

Development of Position Statement

An exhaustive review of the literature was performed using electronic databases (MEDLINE, PubMed, and Ovid; key words included "inflammatory bowel disease," "ulcerative colitis," and "Crohn's disease"). Standard textbooks with chapters on inflammatory bowel disease were evaluated, and the reference lists were also compiled for all articles to obtain references before a preliminary document was drafted. The preliminary draft was then reviewed by the Clinical Practice and Economics Committee of the American Gastroenterological Association.

Grading of Recommendations

This position statement conforms to the American Gastroenterological Association guidelines for evidence-based position statement development. The grading of each recommendation is dependent on the category of evidence supporting it.

The quality of evidence on which a recommendation is based is as follows.

Grade A: Homogeneous evidence from multiple well-designed, randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power.

Grade B: Evidence from at least 1 large well-designed, clinical trial with or without randomization from cohort or case-control analytic studies or well-designed meta-analysis.

Grade C: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

General Principles of Medical Therapy for IBD

The treatment of patients with CD and UC is dependent on several distinct factors, including disease location (eg, ileocecal vs colonic or proctitis vs pancolitis), severity (mild, moderate, or severe), and complications. The treatment of patients should be individualized based on the patient's prior symptomatic response and tolerance to specific medical therapies. Therapy is sequential to treat acute disease and then to maintain remission. Surgery is appropriate for obstructing stenoses, cancerous or precancerous lesions, suppurative complications, or medically refractory disease. The use of narcotic analgesics should be avoided except for the treatment of patients in the perioperative setting, given

Abbreviations used in this paper: ATI, antibodies to infliximab; AZA, azathioprine; CI, confidence interval; CIR, controlled ileal release; ECCDS, European Cooperative Crohn's Disease Study; FDA, Food and Drug Administration; MMF, mycophenolate mofetil; 6-MP, 6-mercaptopurine; 6-MMP, 6-methylmercaptopurine; NCCDS, National Cooperative Crohn's Disease Study; OR, odds ratio; 6-TGN, 6-thioguanine nucleotide; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase.

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the potential for tolerance and abuse in the setting of chronic disease.

Medications Used for the Treatment of Patients With IBD

The current status of therapy for IBD is rapidly evolving, with many new biologic agents under investigation. In the forthcoming sections, the data that support the use of immunomodulators in IBD are reviewed. The use of corticosteroids, azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, mycophenolate mofetil (MMF), cyclosporine, tacrolimus, and infliximab in particular are reviewed in both UC and CD. Aminosalicylates and antibiotics are not discussed.

Corticosteroids

Corticosteroids include parenteral, oral, and topical agents. Examples of oral corticosteroids include prednisolone, prednisone, and budesonide, whereas parenteral agents include intravenous (IV) hydrocortisone, adrenocorticotropic hormone, and methylprednisolone. Corticosteroids, when used orally or parenterally, are potent anti-inflammatory agents for the acute treatment of patients with moderate to severe relapses of IBD. Budesonide (Entocort; AstraZeneca Pharmaceuticals, Wayne, PA) is a highly potent corticosteroid with limited systemic bioavailability due to extensive first-pass hepatic metabolism. Enteric preparations with distal small intestinal and proximal colonic release can produce therapeutic benefit with reduced systemic toxicity in ileocecal CD. Topical agents in the form of suppositories or foam have been used to treat patients with proctitis, whereas enemas are effective in patients with disease up to the splenic flexure. The mechanism of action of corticosteroids is not discussed here in detail given recent reviews of these data.³⁻⁹ The use of corticosteroids in patients with IBD is intended to reduce inflammatory mediators through binding of the glucocorticoid receptor expressed by immune cells. Binding of glucocorticoids to their receptors results in the trans-repression of proinflammatory transcription factors such as nuclear factor κ B and apoptosis of target inflammatory cells and activated lymphocytes.^{10,11} Choice of corticosteroid should be based on which has the greatest glucocorticoid activity compared with its mineralocorticoid activity.

Mild to moderate IBD. The use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate to severe disease. An exception would be patients who have failed to respond to first-line therapies for IBD such as mesalamine for UC or antibiotics for CD in whom corticosteroids are used

because of the absence of effective, less toxic medications. Controlled ileal release (CIR) budesonide (Entocort) is indicated for the treatment of patients with mild to moderate ileal and right-sided colonic CD. Enteric-coated budesonide has not been shown to be more effective than placebo in patients with distal UC.¹² Indeed, even patients with CD who have distal colon or rectal involvement respond less well to enteric-coated budesonide than to conventional prednisone (remission, 47% vs 62.5%), suggesting this therapy is most efficacious in those with ileal and right-sided colonic involvement.¹³

Budesonide is a topically active glucocorticoid structurally related to 16-hydroxyprednisolone.^{14,15} Budesonide has a very high affinity for the glucocorticoid receptor (15 times that of prednisolone and 195 times that of hydrocortisone). The majority of the drug is converted by the cytochrome P-450 system in the liver to inactive metabolites, with only 10%–15% of the drug reaching the systemic circulation. The current preparation of budesonide (Entocort) available in the United States is formulated to allow the slow release of the drug, mainly in the ileum and the right side of the colon.¹⁶⁻¹⁸ The Entocort capsule contains microcapsules made of an inner sugar core surrounded by budesonide in ethylcellulose and an outer acrylic-based resin coating (Eudragit; Rohm America, Piscataway, NJ) that dissolves at a pH of ≥ 5.5 . Fifty-two percent to 70% of the CIR budesonide formulation is absorbed in the ileocolonic region, with a mean absorption time of 6.4 hours and a systemic bioavailability of 9% in healthy volunteers. The improved toxicity profile (discussed in the following text) of this agent compared with conventional corticosteroids relates to its low systemic bioavailability.

Level A evidence supports the use of CIR budesonide for induction of remission of ileocolonic CD. First, CIR budesonide at a dosage of 9 mg/day is more effective than placebo at inducing remission (51% vs 20%) at 8 weeks (Table 1).¹⁹ CIR budesonide at a dosage of 9 mg/day is also more effective than mesalamine (Pentasa; Shire Pharmaceuticals, Wayne, PA) at a dosage of 4 g/day (69% vs 45% at 8 weeks).²⁰ The time to onset of action with CIR budesonide is approximately 2 weeks. Trials comparing oral budesonide with prednisolone show comparable efficacy for inducing remission in active CD.^{13,21-23} In a meta-analysis comparing CIR budesonide with prednisolone, patients with moderate to severe disease (Crohn's Disease Activity Index [CDAI] scores >300) were less likely to respond to CIR budesonide.²⁴ Because the side effect profile is superior to that of conventional corticosteroids (discussed in the following text), CIR budesonide may be considered first-line therapy for patients with mild to moderate ileal and right-sided colonic disease.

Table 1. Short-term Efficacy of Corticosteroids in IBD

Type of IBD	n	Interventions tested	Response/remission	Period of study	P value	References
Mild to moderate active IBD						
CD (ileocecal)	67	Bud 3 mg daily	Remission	8 wk	<.001 (9 mg vs placebo)	Greenberg et al, 1994 ¹⁹
	61	Bud 9 mg daily	33%			
	64	Bud 15 mg daily	51%			
	66	Placebo	43%			
CD (ileocecal)	80	Bud 9 mg daily	Remission	8 wk	<.05 (Bud groups vs placebo)	Tremaine et al, 2002 ³¹³
	79	Bud 4.5 mg BID	48%			
	41	Placebo	53%			
CD (ileocecal)	91	Bud 9 mg daily	Remission	16 wk (primary end point, 8 wk)	.001	Thomsen et al, 1998 ²⁰
	83	Mesalamine 2 g BID	69%			
CD (ileocecal)	88	Bud 9 mg daily	Remission	8 wk	NS	Rutgeerts et al, 1994 ²¹
	88	Prednisolone 40 mg daily then tapered	45%			
	88	Prednisolone 40 mg daily then tapered	52%			
CD (ileocecal)	58	Bud 9 mg daily	Remission	8 wk	NS	Campieri et al, 1997 ²³
	61	Bud 4.5 mg BID	60%			
	58	Prednisolone 40 mg daily then tapered	42%			
CD (ileocecal)	34	Bud 3 mg TID	Remission	8 wk	NS	Gross et al, 1996 ²²
	33	Prednisolone 48 mg daily then tapered	56%			
CD (ileocecal)	100	Bud 3 mg TID	Remission	8 wk	NS	Bar-Meir et al, 1998 ¹³
	101	Prednisone 40 mg daily then tapered	72.7%			
Moderate to severe						
CD	85	Prednisone 0.5–0.75 mg · kg ⁻¹ · day ⁻¹	Remission	17 wk	.0001 (prednisone vs placebo)	Summers et al (NCCDS), 1979 ³⁶
	77	Placebo	60%			
	59	AZA 2.5 mg/kg	30%			
	74	Sulfasalazine 1 g/15 kg	40%			
CD	47	Methylprednisolone 48 mg/day (tapered by 8 mg/wk)	Remission	18 wk	<.001 for prednisolone, <.05 for sulfasalazine, <.001 for combination compared with placebo	Malchow et al (ECCDS), 1984 ³⁷
	54	Sulfasalazine 3 g/day	83%			
	56	Methylprednisolone + 3 g/day Sulfasalazine	50%			
	56	Methylprednisolone + 3 g/day Sulfasalazine	78%			
	58 (active disease group)	Placebo	38%			
CD ^a	109	Population-based Prednisolone 1 mg · kg ⁻¹ · day ⁻¹	Complete remission, 48% Partial response, 32% No response, 20%	30 days	N/A	Munkholm et al, 1994 ⁴¹
CD ^b	173	Population-based Prednisone 40–60 mg/day	Complete remission, 58% Partial response, 26% No response, 16%	30 days	N/A	Faubion et al, 2001 ⁴⁰

UC ^c	109	Cortisone 100 mg/day	Remission, 41.3% Partial response, 27.5%	6 wk	<.001	Truelove and Witts, 1954, 1955 ^{42,43}
	101	Placebo	Remission, 15.8% Partial response, 24.8%			
UC ^c	58	Prednisolone 5 mg 4 times daily + hydrocortisone enema 100 mg	Remission 76%	2 wk	<.05	Truelove et al, 1962 ⁴⁴
	60	Sulfasalazine 2 g 4 times daily for first wk, 1 g 4 times daily second wk	52%			
UC	20	Prednisone 60 mg	Remission, 13/20 (65%) Partial response, 6/20 (30%)	5 wk	<.01 for 2 higher doses compared with 20 mg/day	Baron et al, 1962 ⁶⁶
	20	Prednisone 40 mg	Remission, 13/20 (65%) Partial response, 1/20 (5%)			
	20	Prednisone 20 mg (all doses divided TID or 4 times daily)	Remission, 6/20 (30%) Partial response, 3/20 (15%)			
UC ^b	185	Population-based Prednisone 40–60 mg/day	Complete remission, 54% Partial response, 30% No response, 16%	30 days	N/A	Faubion et al, 2001 ⁴⁰
Severe UC ^c	149	Prednisolone 60 mg/day IV + hydrocortisone 100 mg rectally	Remission, 64% Partial response, 13% No response, 23%	5 days	N/A	Truelove et al, 1974, 1978 ^{46,47}
UC ^d	32	Corticotropin (ACTH) 120 U/day	Overall remission 42%	10 days	.025	Meyers et al, 1983 ⁴⁸
	34	Hydrocortisone 300 mg/day IV	No prior corticosteroids: ACTH, 63% Hydrocortisone, 28% Prior corticosteroids: ACTH, 25% Hydrocortisone, 53%		.05	
CD	44	ACTH 120 U/day IV	ACTH, 82%	10 days	NS	Chun et al, 1998 ⁵³
	44	Hydrocortisone 300 mg/day IV	Hydrocortisone, 93%			

NOTE. Unless otherwise stated, remission for CD is defined as a CDAI score <150 and response is defined as a decrease in CDAI of >70 points.

Bud, budesonide; BID, twice daily; TID, 3 times daily.

^aCorticosteroid dosing was prednisolone 1 mg/kg body wt per day, reduced within weeks to a maintenance dose of 10–15 mg and kept at that level for 3–5 months.

^bThe initial dosages of prednisone ranged from 40 to 60 mg/day, and individual treating physicians attempted prednisone taper over a variable period of 3–6 months. Short-term 30-day responses for both studies were defined as follows. Complete remission: total regression of clinical symptoms declining to ≤2 bowel movements/day; no blood, pus, or mucus in feces; no abdominal pain, fever, weight loss, and extraintestinal symptoms. Partial remission: regression of clinical symptoms declining to ≤4 stools/day; blood, pus, mucus in feces; or abdominal pain or all 4 less than daily and no systemic symptoms as fever and weight loss. No response: no regression of clinical symptoms.

^cFor UC studies by Truelove et al, remission was defined as 1–2 stools/day, no blood, no fever, no tachycardia, hemoglobin normal or returning toward normal, erythrocyte sedimentation rate normal or returning toward normal, and gaining weight. Partial remission was defined as intermediate between remission and no response.

^dTherapeutic success was defined as the absence of all symptoms and the reduction of the frequency of bowel movements to <2 per day. All other cases were classified as therapeutic failures. Also, if after the fourth day of treatment there was continuous fever of ≥37.5°C or colonic dilation on radiography, the study period was terminated early and the study treatment recorded as a failure.

Topical therapy with either conventional corticosteroids or budesonide is effective for distal colonic inflammation. In 2 meta-analyses, topical corticosteroids were found to be less effective than topical mesalamine for inducing remission of distal UC.^{25,26} In placebo-controlled trials, mesalamine enemas achieve remission rates between 60% and 70% at dosages between 1 and 4 g/day at 4 weeks of treatment. By contrast, 4-week remission data for corticosteroid enema preparations range between 30% and 40%.²⁶ However, the combination of topical corticosteroids with topical mesalamine is often more efficacious than either alone in the short-term treatment of patients with distal UC.²⁷ Foam preparations are often better tolerated by patients and may be easier to retain.²⁸ Although absorption of corticosteroids after topical administration is less than after oral administration, prolonged treatment with topical corticosteroids may still be associated with corticosteroid-related side effects.²⁹ In addition to the use of liquid and foam formulations, individuals can use corticosteroid suppositories. In general, suppositories or foams are useful for the treatment of patients with proctitis, whereas foams and enemas are capable of treating patients with more extensive disease reaching to the level of the splenic flexure.

Recently, a new generation of topical corticosteroids (eg, budesonide) has been developed in an attempt to reduce these side effects. Danielsson et al compared budesonide enemas in a dose of 2 mg/100 mL with placebo for active distal colitis or proctitis.³⁰ Budesonide was more effective than placebo without systemic side effects. A separate study showed that dosages of budesonide up to 4 mg/day for 2 weeks had no effect on morning plasma cortisol levels.³¹ Several, but not all, subsequent trials have shown topical budesonide to be as efficacious as prednisolone enemas,³² mesalamine enemas,³³ and systemic corticosteroids³⁴ in the treatment of patients with distal UC. Budesonide enemas are comparable to prednisolone enemas for induction of remission in patients with distal UC.^{32,35} Budesonide enemas are not available in the United States. Additional trials are needed to determine the effect of longer-term use of topical budesonide.

Moderate to severe IBD. Conventional corticosteroids are effective in the short-term induction of remission in patients with UC and CD. In patients with CD, corticosteroids are justified in those with moderate to severe symptoms, regardless of disease location, or those who failed to respond to CIR budesonide for ileocecal CD. There have been 2 major prospective, randomized, placebo-controlled trials showing that corticosteroids are effective agents for induction of remission in patients with CD. The National Cooperative Crohn's

Disease Study (NCCDS)³⁶ randomized 162 patients; 60% achieved remission using oral prednisone 0.5–0.75 mg/kg daily with tapering over 17 weeks compared with 30% in the placebo group (number needed to treat, 3). Similar findings were seen in the European Cooperative Crohn's Disease Study (ECCDS).³⁷ Of the 215 patients who entered the study with active disease (CDAI score >150), 83% were able to achieve clinical remission using oral prednisolone 1 mg/kg daily compared with 38% receiving placebo over 18 weeks (number needed to treat, 2). There was a 92% remission rate within 7 weeks in 142 patients with moderately active CD who were given oral prednisone 1 mg/kg daily without tapering.³⁸ No dose-response studies have been performed in patients with CD. One consideration in patients with CD is decreased oral absorption compared with healthy volunteers.³⁹

In population-based studies, corticosteroids are used in 43% of patients with CD.⁴⁰ In the Olmsted County database, 30-day outcomes following a course of corticosteroids were complete remission in 58%, partial remission in 26%, and no response in 16% (Table 1). The results in Denmark were remarkably similar except that a slightly higher percentage of their inception cohort were given corticosteroids (109/196 [56%]).⁴¹ In the Olmsted County cohort, patients were given prednisone 40–60 mg/day; in Copenhagen, corticosteroids were dosed at 1 mg/kg. The similarity in their results suggests that this dose range for induction of remission is adequate. Budesonide was found to be slightly less active than prednisolone for the treatment of patients with moderate to severe active CD.²⁴

Corticosteroids also have an important role in inducing remission in patients with moderate to severe UC who are intolerant of or who have failed to respond to mesalamine. Truelove and Witts initially described the use of oral cortisone at a dosage of 100 mg/day for the treatment of patients with mild to severely active UC.^{42,43} Truelove et al examined the efficacy of sulfasalazine 8 g/day compared with prednisolone 40 mg/day for the treatment of patients with UC and found a greater likelihood of remission using corticosteroids.⁴⁴ In patients with moderate to severely active UC, adding sulfasalazine to corticosteroids does not result in better efficacy compared with corticosteroids alone.⁴⁵ Using the same population-based Olmsted County cohort, Faubion et al found that approximately one third of patients with UC will require corticosteroid therapy during the course of their disease.⁴⁰ The short-term 30-day outcomes for patients with UC were complete remission in 54%, partial remission in 30%, and no response in 16%. Concurrent use of mesalamine or sulfasalazine was neg-

actively associated with a lack of response to corticosteroids (odds ratio [OR], 0.35; $P = .04$). No differences in short-term outcomes were seen regardless of disease duration, disease extent, or age at diagnosis. The similarity in efficacy for corticosteroids across disease types and diverse populations speaks to the broad, nonspecific anti-inflammatory effect of corticosteroids. For patients with UC without a response to corticosteroids in the short term, the rate of colectomy was 90%.⁴⁰ A distinction between IV or oral corticosteroids was not made in this population-based study. These patients should be considered in the severe category and may benefit from calcineurin inhibitors (discussed in the following text) or biologic agents.

Severe or fulminant IBD. Patients who fail to respond to oral prednisone should be hospitalized and given IV corticosteroids in the form of methylprednisolone (48–60 mg daily) or hydrocortisone (300–400 mg daily) either by continuous or bolus infusion. Methylprednisolone has decreased mineralocorticoid properties compared with hydrocortisone and is currently favored for this reason. Placebo-controlled studies have not been performed because of the high mortality associated with severe attacks of UC. Studies comparing the efficacy in IBD of different types of parenteral corticosteroids have not been performed; however, several studies have compared the efficacy of corticotropin or adrenocorticotrophic hormone (ACTH) compared with hydrocortisone for the treatment of patients with UC.

Truelove et al reported the use of IV hydrocortisone in patients with severe UC.^{46,47} In their pioneering studies, they administered prednisolone at a dosage of 60 mg/day for an average of 5 days and found that 64% of patients entered remission, an additional 13% improved, and 23% had no response and required colectomy. IV corticotropin may be more effective than IV hydrocortisone 300 mg/day for patients with UC who have not received prior corticosteroid treatment,⁴⁸ although adrenal hemorrhage has been reported as a complication of ACTH therapy. Other smaller studies have not shown a benefit of ACTH over hydrocortisone.^{49,50} The general range of response seen with these dosages of corticosteroids in short-term studies (5–14 days) is approximately 50% (ranging from approximately 45%–80%).^{46–48,51} The variability in results is dependent on the severity of disease at baseline and the definitions of response. Prolongation of therapy with parenteral corticosteroids beyond 7–10 days has not been proven to add any benefit and may be deleterious. Alternative biologic agents, immunomodulators, or surgery must be considered for patients failing to respond to parenteral corticosteroids.

Randomized controlled trials of corticosteroids in patients with severe CD have not been performed, but large anecdotal evidence supports its use. In one study, IV therapy resulted in remission in 76% (38/49).⁵² A study comparing ACTH and hydrocortisone 300 mg/day found a high rate of remission with both strategies.⁵³ Given the similarity in treatment efficacy of corticosteroids in moderate to severe disease between UC and CD, it is likely the remission rate in CD for parenteral corticosteroids is similar to that in UC.

Maintenance therapy. Although corticosteroids are effective for induction of remission, they have not been shown to be effective for maintenance of remission and the risks of long-term therapy outweigh their benefits. Patients who require a short-term course of corticosteroids have more aggressive disease as reflected by the statistic that once corticosteroids are initiated, there is a 30% rate of colectomy for UC and 38% rate of surgery for CD within that year (Table 2). Even patients who have a complete response to corticosteroids in the short term have a high rate of surgery within the year. In the Olmsted County data, 12% of patients who were in remission in the short term had a colectomy for UC and 26% had surgery for CD.⁴⁰ At the other extreme, however, were patients with UC or CD who had no response to corticosteroids and a surgery rate of 90%. Corticosteroids have not been shown to be beneficial for maintenance of remission in patients with UC.^{54–56} Oral cortisone 50 mg/day was not effective at maintaining a corticosteroid-induced remission.⁵⁴ Other strategies that have been used include prednisone 15 mg daily (5 mg by mouth 3 times daily) for 6 months.⁵⁵ In this study, the same number of patients maintained remission or experienced a relapse whether taking prednisone (remission, 12/32; relapse, 18/32) or placebo (remission, 12/30; relapse, 17/30), but the prednisone group experienced more side effects. Oral prednisolone 40 mg every other day compared with placebo for 3 months at a time was associated with a reduced number of patients experiencing a relapse⁵⁶ but again was associated with a higher frequency of corticosteroid-related side effects. In light of this, corticosteroids should not be used for maintenance treatment of patients with IBD.

The NCCDS and the ECCDS provided the most complete data on evaluation of the use of prednisone for maintenance of remission in patients with CD.^{36,37} In the NCCDS, the study population consisted of patients who had entered the maintenance phase following a 17-week induction regimen with prednisone, sulfasalazine, AZA, or placebo. A second group included patients who were in remission at the time of enrollment and received 1 of these 4 medications at “maintenance” doses. Of the 85

Table 2. Long-term Outcomes of Corticosteroid Therapy in Prospective and Population-Based Studies

Moderate to severe	No. of patients	Interventions tested	Remission	Time	P values	References
CD	See remission column	Pred 0.25 mg · kg ⁻¹ · day ⁻¹ Placebo AZA 1 mg/kg Sulfa 0.5 g/15 kg	Remission (year 1 and year 2, respectively): Part 1 (<i>baseline CDAI score >150</i>) Pred: 21/59 (36%) and 11/35 (31%) Placebo: 14/76 (18%) and 6/52 (12%) AZA: 15/54 (28%) and 7/34 (21%) Sulfa: 16/53 (30%) and 5/32 (16%) Part 2 (<i>baseline CDAI score <150</i>) Pred: 35/61 (57%) and 12/37 (32%) Placebo: 65/101 (64%) and 23/57 (40%) AZA: 37/54 (69%) and 10/35 (29%) Sulfa: 36/58 (62%) and 12/39 (31%)	1 and 2 y Part 2	Part 1 Pred: .001, .003; AZA: .292, .68; Sulfa: .147, .825 compared with placebo All NS compared with placebo	Summers et al, 1979 (NCCDS) ³⁶
CD	113	Methylprednisolone 8 mg/day	57% and 42%	1 and 2 y	<.001 for Pred and combination, <.05 for Sulfa compared with placebo	Malchow et al, 1984 (ECCDS) ³⁷
	117	Sulfa 3 g/day	43% and 33%			
	112	Methylprednisolone + 3 g/day Sulfasalazine	50% and 39%			
	110	Placebo	30% and 22% (% of patients failure- or relapse-free at 1 and 2 years; includes patients entering active and in remission)			
CD ^a	109	Population-based	Response off corticosteroids, 55%	1 y	N/A	Munkholm et al, 1994 ⁴¹
			Corticosteroid dependent, 45% Surgical resection (21%): ● 26% corticosteroid dependent ● 59% corticosteroid refractory			
CD ^b	172	Population-based	Response off corticosteroids, 32% Corticosteroid dependent, 28% Surgical resection, 38%	1 y	N/A	Faubion et al, 2001 ⁴⁰
UC	109	Cortisone (dose range, 100 mg/day for 6 weeks or 100 mg/day for 2–3 weeks tapered to 50–75 mg/day for remainder of 6 weeks)	<i>Symptom-free for 9 mo</i> : First attack of UC: Cortisone, 21/43 (48.8%) Placebo, 8/38 (21.1%)	9 mo	First attack: <.02 Relapsed: NS	Truelove and Witts, 1955 ⁴³
	101	Placebo	Relapsed UC: Cortisone, 23/64 (35.9%) Placebo, 26/60 (43.3%) <i>Ileostomy rate</i> : Cortisone, 9/107 (8.3%) Placebo, 15/98 (14.9%)			
UC	185	Population-based	Response off corticosteroids, 49% Corticosteroid dependent, 22% Colectomy 29%	1 y	N/A	Faubion et al, 2001 ⁴⁰

NOTE. Patients in the NCCDS and ECCDS were followed up for 1 and 2 years following induction of remission or entry into the study in remission. The percentages refer to the patients still in remission at the end of 1 and 2 years.

Pred, prednisone; Sulfa, sulfasalazine.

^aCorticosteroid dosing was prednisolone 1 mg/kg body wt per day, reduced within weeks to a maintenance dose of 10–15 mg and kept at that level for 3–5 months. Thirty days after prednisolone treatment had finished, irrespective of its length, the following outcome categories were defined: prolonged response, maintenance of complete remission or partial remission after treatment had finished; dependence, relapse within 30 days after treatments had finished or relapse at dose reduction impeding discontinuation of prednisolone treatment for more than 1 year.

^bOutcomes at 1 year were defined as follows. Prolonged response: maintenance of complete or partial remission after corticosteroid therapy was completed; patients who required subsequent courses of corticosteroids but maintained complete or partial response and were corticosteroid free at the end of 1 year were included in the prolonged response outcome group. Corticosteroid dependent: continued corticosteroid therapy at year end caused by relapse after corticosteroids were discontinued or caused by relapse at dose reduction impeding discontinuation of corticosteroid therapy; patients who required surgical resection (see below) and were also corticosteroid dependent at 1 year were counted in the surgical resection group. Surgical resection: relapse within 1 year after corticosteroid therapy was initiated, resulting in surgical resection.

patients who entered the study with active disease and were treated with corticosteroids, 28 were available to enter the maintenance phase of the study in which they were treated with prednisone $0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. By comparison, of the 77 patients who were given placebo for 17 weeks, 20 patients entered the maintenance phase and were continued on placebo. At the end of 1 year, 21 of the 28 patients (75%) who received prednisone and 14 of the 20 patients (70%) who received placebo were still in remission ($P = .001$). A second cohort of 274 patients was entered directly into the maintenance phase of the NCCDS without the 17-week induction phase. These patients were assigned to receive placebo, sulfasalazine 500 mg/day , prednisone $0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, or AZA $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. None of these strategies proved superior to placebo at 1 year in prevention of clinical relapse or need for surgery.

In the ECCDS, 452 patients were randomized to receive prednisolone 48 mg/day (followed by a tapering regimen), sulfasalazine 3 g/day , a combination of the two, or placebo. At the end of 1 year, approximately 57% of patients treated with prednisolone remained relapse-free compared with 50% in the combination group, 43% in the sulfasalazine group, and 30% in the placebo group ($P < .001$ for prednisolone and combination therapy, $P < .05$ for sulfasalazine compared with placebo). Although there appears to be a benefit to corticosteroids alone or in combination with sulfasalazine for maintenance, if only looking at the patients who entered the study in remission (CDAI score <150), there was no difference compared with placebo for any intervention. These data can be interpreted in a variety of ways. The finding that patients were "maintained" on corticosteroids if their disease was induced by corticosteroids probably means that these patients were in fact corticosteroid dependent. For patients with CD in remission, the data do not support initiation of corticosteroids to prevent a relapse, even at high doses of corticosteroids.

Corticosteroid dependence differs from maintenance therapy. A true maintenance therapy should demonstrate a dose response in a population of patients and prevent disease recurrence. Corticosteroid dependence refers to the inability of a particular patient to taper below a certain dose of corticosteroid without flaring. In the Olmsted County data, approximately one fourth of patients with either UC or CD were steroid dependent at the end of 1 year.⁴⁰ The Danish cohort revealed similar findings, with 40% of patients with CD becoming corticosteroid dependent.⁴¹ To a certain extent, these distinctions are semantic because for a given patient who is corticosteroid dependent, there is usually a dose of corticosteroid that maintains the patient in clinical remis-

sion. Immunomodulators and/or infliximab are indicated for patients who cannot taper corticosteroids without flaring.

The observation that corticosteroids are effective in inducing short-term remission but have unacceptable long-term consequences may have several explanations. First, the need to administer corticosteroids is likely to indicate that a patient has more severe disease. The second is that corticosteroids do not alter the natural history of disease. In particular, corticosteroids do not reliably result in endoscopic healing of the mucosa in patients with CD.³⁸ In a study of 142 patients with CD treated with prednisone $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for up to 7 weeks, 92% went into clinical remission whereas only 29% had endoscopic remission.³⁸ In the NCCDS, of the 85 patients who received prednisone as induction therapy, 49 patients completed the 17-week study in remission (CDAI score <150). Of these 49 patients, 9 were excluded from further participation because of worsening on their barium radiographs, suggesting that even patients in a corticosteroid-induced clinical remission can have their disease progress.

In patients with UC, topical budesonide appears to be superior to topical prednisolone at achieving endoscopic healing (52% vs 24%).³⁰ Oral budesonide 10 mg/day in a preparation that achieves colonic delivery and prednisolone 40 mg/day were similarly effective at improving endoscopic appearance in patients with UC, but the rates of endoscopic healing (sigmoidoscopy score of 0) were low in both groups (4/31 and 6/36, respectively).¹² Data on endoscopic healing in UC with parenteral corticosteroids is limited. The original studies by Truelove and Witts on oral cortisone for the treatment of patients with mild to severe UC showed that treatment with cortisone resulted in normal or near-normal findings on sigmoidoscopy in 19 of 63 patients compared with 6 of 57 patients receiving placebo.^{42,43} In the same study, 14 of 26 patients in the cortisone group and 19 of 25 patients in the control group had no change or worsening on barium radiographic examination. It is likely that agents that result in endoscopic healing will alter the natural history of IBD with respect to need for hospitalization, surgery, or development of cancer, but these correlates are currently unproven.

Because of its favorable side effect profile, budesonide EC has been examined for maintenance of remission in patients with ileocecal CD following induction therapy with budesonide or conventional corticosteroids (Table 3). Budesonide has a limited role in maintenance of remission. None of the studies have shown a significant benefit at 1 year.⁵⁷⁻⁶¹ Greenberg et al conducted a 1-year, randomized, double-blind, placebo-controlled trial using

Table 3. Results of Randomized Placebo-Controlled Trials of Budesonide for the Maintenance of Remission in CD

References	Type of remission	Comparison groups	Follow-up duration (y)	Efficacy	
				Remission rates at 1 year	Time to relapse
Greenberg et al, 1996 ⁵⁷	Medical	Budesonide 3 and 6 mg daily vs placebo	1	No difference	6 mg, 178 days 3 mg, 124 days Placebo, 39 days
Lofberg et al, 1996 ⁵⁸	Medical	Budesonide 3 and 6 mg daily vs placebo	1	No difference	6 mg, 258 days 3 mg, 139 days Placebo, 92 days
Ferguson et al, 1998 ⁵⁹	Medical	Budesonide 3 and 6 mg daily vs placebo	1	No difference	No difference
Gross et al, 1998 ⁶⁰	Medical	Budesonide 1 mg 3 times daily vs placebo	1	No difference	No difference
Hanauer et al, 2005 ⁶¹	Medical	Budesonide 6 mg daily vs placebo	1	No difference	6 mg, 360 days Placebo, 169 days ($P = .132$)
Hellers et al, 1999 ⁶⁴	Surgical	Budesonide 6 mg daily vs placebo	1	Budesonide efficacious only in patients whose indication for surgery was for active inflammation	
Ewe et al, 1999 ⁶³	Surgical	Budesonide 1 mg 3 times daily vs placebo	1	No difference	No difference

budesonide 3 mg daily and 6 mg daily.⁵⁷ Patients receiving budesonide 6 mg daily had a median time to relapse or discontinuation of therapy of 178 days compared with 124 days in those receiving budesonide 3 mg and 39 days in those receiving placebo. However, at 1 year, the rates of relapse in the 3 groups were similar. In a similar randomized, double-blind, controlled trial by Lofberg et al, the same dosages of budesonide were evaluated for maintenance of remission.⁵⁸ In the dosages studied (3 mg, 6 mg, and placebo), there were no differences in remission rates observed at 1 year between the groups. However, at 3 months, only 19% of patients treated with budesonide (6 mg daily) had experienced a relapse compared with 45% in the 3-mg group and 44% in the placebo group. In a third study by Ferguson et al from the Global Budesonide Study Group, the efficacy and safety of budesonide for maintenance of remission in 75 patients with ileal or ileocolonic CD was assessed.⁵⁹ The patients received either placebo or budesonide at dosages of 3 mg or 6 mg daily for 12 months. There were no statistically significant differences observed among the 3 groups (placebo, 3 mg daily, or 6 mg daily) at 12 months with respect to relapse rate. In another study, Gross et al reported similar results using budesonide (1 mg 3 times daily) versus placebo.⁶⁰ As distinct from the maintenance studies by Lofberg et al and Greenberg et al, these last 2 studies failed to show a prolongation in median time to relapse.^{59,60} Finally, an American study found a prolongation in time to relapse in patients treated with budesonide EC 6 mg/day compared with placebo (360 vs 169 days).⁶¹

A meta-analysis of 4 double-blind, placebo-controlled, 12-month trials showed that patients (380 patients total) maintained on budesonide EC 6 mg/day had a longer time in remission compared with placebo or budesonide EC 3 mg/day (268 days for budesonide 6 mg/day compared with 170 days for budesonide 3 mg and 154 days for placebo).⁶² In pairwise comparisons, budesonide 6 mg/day was significantly superior to placebo ($P = .0024$); there was a trend toward significance when compared with budesonide 3 mg/day ($P = .052$). The proportion of patients experiencing a relapse was significantly lower ($P < .05$) for the patients treated with budesonide 6 mg/day at 3 months (25%) and 6 months (37%) than for the patients treated with budesonide 3 mg/day (39% at 3 months, 51% at 6 months) and placebo (40% at 3 months, 50% at 6 months). The proportion of patients experiencing a relapse at 1 year was lower for budesonide (51%) than for placebo (59%) but did not reach statistical significance. Overall, the incidence of adverse events and serious adverse events was not significantly different among the 3 treatment groups, although moon face (7.6% budesonide, 2.1% placebo) and acne (10.3% budesonide, 4.2% placebo) were more common in patients treated with budesonide 6 mg/day than patients receiving placebo ($P < .05$). The investigators thus concluded that budesonide 6 mg/day prolongs time to relapse for patients with CD versus placebo.

Similar to the findings in medically induced remission, budesonide EC prolongs surgically induced remis-

sion but does not change the percentage of patients free of clinical or endoscopic relapse at 1 year.^{63,64}

One of the concerns related to use of budesonide EC as maintenance therapy relates to the fact that it does not lead to endoscopic healing. Mantzaris et al performed a study on 67 patients with CD with corticosteroid-induced remission and compared budesonide EC 6–9 mg/day with AZA 2.2 mg · kg⁻¹ · day⁻¹.⁶⁵ Although both strategies were comparably effective at maintaining clinical remission at the end of 1 year, only AZA resulted in improvement in the CD endoscopic index of severity. Thus, the long-term benefits of budesonide as maintenance therapy are unclear. Budesonide EC monotherapy may be considered in patients with mild to moderate disease who are intolerant of immunomodulators or biologic agents.

Dosing and tapering for IBD. Few dose-ranging studies are available to determine the most efficacious dosage of corticosteroids in the treatment of patients with IBD. In population-based studies, prednisone 40–60 mg/day or 1 mg · kg⁻¹ · day⁻¹ achieved remission in approximately 50% of patients. Studies comparing 3 dosages of prednisone (20, 40, and 60 mg/day) in patients with UC found that the 2 higher dosages were more effective than a dosage of 20 mg/day; a dosage of 60 mg/day was associated with a higher likelihood of corticosteroid-related toxicity but not significantly greater efficacy than a dosage of 40 mg/day.⁶⁶ This study, however, was underpowered to determine inferiority of a dosage of 40 mg/day compared with a dosage of 60 mg/day. A small study found that in patients with UC, splitting the dose of prednisone every 6 hours is not more effective than once-daily dosing.⁶⁷ In terms of parenteral prednisolone, administration by continuous infusion rather than bolus infusion results in higher plasma concentrations but has not been shown to be more effective.⁶⁸ No dose-ranging studies have been performed in patients with CD, but in prospective studies prednisone 1 mg · kg⁻¹ · day⁻¹ achieves a high rate of remission.³⁸

The current evidence suggests that the algorithm used for corticosteroid tapering after achieving an initial response is unlikely to influence the long-term outcome in patients with CD or patients with UC. In the NCCDS, the dosage of prednisone was adjusted during the 17-week induction period based on the severity of disease activity as measured by the CDAI (0.75 mg · kg⁻¹ · day⁻¹ for a CDAI score of 300, 0.5 mg · kg⁻¹ · day⁻¹ for a CDAI score between 150 and 300, and 0.25 mg · kg⁻¹ · day⁻¹ for a CDAI score of 150).³⁶ In the ECCDS,³⁷ 6-methylprednisolone was given initially and then there was a 6-week corticosteroid tapering regimen: 48 mg/day in week 1 tapered to 32

mg/day in week 2, 24 mg/day in week 3, 20 mg/day in week 4, 16 mg/day in week 5, and finally 12 mg/day in week 6. In patients who received placebo after induction of remission, about 35% remained in remission at 2 years. In another study (the Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif [GETAID] study),⁶⁹ the initial dosage of corticosteroid was prednisone 1 mg · kg⁻¹ · day⁻¹ for 3–7 weeks. Those who responded clinically but did not have endoscopic responses were randomized to receive either another 5 weeks of corticosteroid therapy or begin corticosteroid tapering immediately. Those who responded both endoscopically and clinically began corticosteroid tapering immediately. The schedule for tapering of prednisone was to taper 10 mg every 10 days until a dosage of 0.5 mg · kg⁻¹ · day⁻¹ and then by 5 mg every 10 days thereafter until medication was discontinued. This tapering regimen in a 70-kg patient would last about 16 weeks. All 3 groups that were evaluated had comparable ability to maintain remission (rates of about 30%–40% at 18-month follow-up). In a subsequent placebo-controlled trial assessing the efficacy of mesalamine in the maintenance of remission (GETAID study),⁷⁰ the same induction regimen and corticosteroid-tapering regimen were used, and the remission rate at 1 year was 36% in the placebo group. Thus, despite the wide variations in these corticosteroid-tapering regimens, none appear to have led to a more favorable long-term outcome compared with placebo. In the case of corticosteroids, an argument may be made that endoscopic remission should not be the basis of tapering the dosage.

In a prospective, randomized, controlled corticosteroid-tapering study,⁷¹ patients with active CD were studied to assess whether the rate of corticosteroid tapering influences the rate of relapse. The 2 groups of patients in the study initially received prednisolone 40 mg/day intramuscularly (IM) for 3 weeks. In 1 group, the corticosteroids were then tapered off in 1 week. In the second group, the dosage of prednisolone was tapered to 30 mg/day IM for 3 weeks, 20 mg/day IM for 3 weeks, 12 mg/day IM for 3 weeks, and finally 8 mg/day IM for 3 weeks. The relapse rates at 6 months were identical in the 2 groups. Thus, the available evidence does not justify a protracted taper of conventional corticosteroids in patients with IBD.

Finally, budesonide has been studied as an alternative to conventional corticosteroids in patients who are corticosteroid dependent. Cortot et al studied 120 patients who had failed to taper their dosage of prednisolone without flaring after 2 attempts.⁷² The mean dosage of prednisolone was 15–17 mg/day at study entry. Patients were randomized to receive placebo or budesonide 6

Table 4. Adverse Effects of Corticosteroids

Type of IBD	n	Interventions tested	Time	Overall AEs	Corticosteroid-related side effects									
					Overall	Moon face	Acne	Hirsutism	Psychosis/mood swings					
CD (ileocecal)	67	Bud 3 mg daily	8 wk	81%	15%	Bud, 7%; placebo, 2% (<i>P</i> = .001)	ND	ND	NR					
	61	Bud 9 mg daily		90%	26%									
	64	Bud 15 mg daily		88%	38%									
	66	Placebo		76% (all NS)	26% (all NS compared with placebo)									
CD (ileocecal)	80	Bud 9 mg daily	8 wk	ND for overall AEs (93%, 91%, 94%, respectively) Early termination due to AEs: Bud 9 mg daily, 6/80; Bud 4.5 mg BID, 8/79; placebo, 3/41 (NS)	ND (specific data not provided)	NR	NR	NR	NR					
	79	Bud 4.5 mg BID												
	41	Placebo												
CD (ileocecal)	91	Budesonide 9 mg daily	16 wk	63% SAEs, 13%; 72% SAEs, 25% ^a (<i>P</i> = .04)	NR	NR	NR	NR	NR					
	89	Mesalamine 2 g BID												
CD (ileocecal)	88	Bud 9 mg daily	8 wk		Bud, 29/88 (33%)	Bud, 15/88	Bud, 5/88	Bud, 2/88	NR					
	88	Pred 40 mg daily then tapered			Pred, 48/88 (55%) (<i>P</i> = .003)	Pred, 31/88	Pred, 20/88	Pred, 2/88						
CD (ileocecal)	58	Bud 9 mg daily	8 wk	Bud 9 mg, 78%	Weight gain: Bud 9 mg, 1 kg	Higher in Pred group (specific numbers NR)	NR	NR	NR					
	61	Bud 4.5 mg BID		Bud 4.5 mg BID, 90%						Bud 4.5 mg BID, 0				
	58	Pred 40 mg daily then tapered		Pred, 90%						Pred, 2.1 kg (<i>P</i> < .0001)				
CD (ileocecal)	35	Bud 3 mg TID	8 wk	Bud, 11/35 (31.4%)	Bud, 10/35 (28.6%)	Bud, 5/35 (14%)	Bud, 5/35 (14%)	Bud, 5/35 (14%)	Bud, 7/35 (20%)					
	33	Pred 48 mg daily then tapered		Pred, 24/33 (72.7%)	Pred, 23/33 (69.7%) (<i>P</i> = .0015)	Pred, 16/33 (48%)	Pred, 16/33 (48%)	Pred, 16/33 (48%)	Pred, 10/33 (30%)					
CD (ileocecal)	100	Bud 3 mg TID	8 wk	ND	Bud, 14%	Bud, 16/100	Bud, 19/100	Bud, 2/100	Bud, 10/100					
	101	Prednisone 40 mg daily then tapered			Prednisone, 30% (<i>P</i> = .006)	Prednisone, 33/101 (<i>P</i> < .05)	Prednisone, 29/101 (<i>P</i> < .05)	Prednisone, 8/101 (<i>P</i> < .05)	Prednisone, 16/101 (<i>P</i> < .05)					
CD (ileocecal)	427	Bud 9 mg/day	8 wk	NR	NR	11%	15%	5%	NR					
	145	Pred 40 mg/day				37% ^a	23% ^a	3%						
	107	Placebo				4%	13%	2% (<i>P</i> = NS)						
CD (ileocecal)	138	Bud 6.8 mg/day (mean)	2 y	96% (SAEs, 35%)	51%	9%	15%	7%	17%					
	134	Pred 14.9 mg/day (mean)		98% (SAEs, 29%)	71% (<i>P</i> < .001)	33% ^a (<i>P</i> < .0001)	26% ^a (<i>P</i> = .026)	13% (NS)	25% (NS)					
CD (active)	85	Prednisone 0.5–0.75 mg · kg ⁻¹ · day ⁻¹	17 wk	Prednisone, 27/85 (32%)	NR	Prednisone, 47%	Prednisone, 30%	Prednisone, 7%	Prednisone, 2%					
	77	Placebo								Placebo, 5/77 (6%)	Placebo, 3%	Placebo, 7%	Placebo, 1%	Placebo
	59	AZA 2.5 mg/kg								AZA, 19/59 (32%)	AZA, 3%	AZA, 18%	AZA, 0%	
	74	Sulfa 1 g/15 kg								Sulfa, 10/74 (14%) (moderate-severe AEs)	Sulfa, 8% (<i>P</i> < .05 for prednisone)	Sulfa, 8% (<i>P</i> < .05 for prednisone or AZA)	Sulfa, 0% (<i>P</i> < .05 for prednisone)	
CD (maintenance)	89	Prednisone 0.25 mg · kg ⁻¹ · day ⁻¹	2 y	Prednisone, 16/61 (26%)	NR	Prednisone, 25%	Prednisone, 19%	Prednisone, 8%	Prednisone, 3%					
	121	Placebo								Placebo, 8/101 (8%)	Placebo, 3%	Placebo, 21%	Placebo, 1%	Placebo, 0%
	73	AZA 1 mg/kg								AZA, 11/54 (20%)	AZA, 2%	AZA, 8%	AZA, 0%	AZA, 0%
	77	Sulfa 0.5 g/15 kg								Sulfa, 7/58 (12%) (moderate-severe AE's)	Sulfa, 7% (<i>P</i> < .05 for prednisone)	Sulfa, 9% (<i>P</i> < .05 for sulfa/AZA compared with placebo)	Sulfa, 0% (<i>P</i> < .05 for prednisone)	Sulfa, 2% (<i>P</i> = NS)

Corticosteroid-related side effects

Hypertension	Cataracts	Striae	Respiratory infection/sepsis	Ankle edema	Petechial bleeding	Easy bruising	Buffalo hump	Adrenocortical axis	References
NR	NR	NR	ND	ND	NR	NR	ND	Cosyntropin stimulation abnormal in 50% of those treated with 9 mg/day compared with 19% for placebo ($P = .006$) Cortisol levels decreased for 9-mg dose and 15-mg dose; no change for 3-mg dose and placebo	Greenberg et al, 1994 ¹⁹
NR	NR	NR	NR	NR	NR	NR	NR	Normal adrenal function: Bud (both), 53%; placebo, 83% ($P < .01$)	Tremaine et al, 2002 ³¹³
NR	NR	NR	NR	NR	NR	NR	NR	Abnormal cosyntropin stimulation in 10% of Bud-treated patients and none of mesalamine-treated patients ($P = .02$)	Thomsen et al, 1998 ²⁰
NR	NR	Bud, 0/88 Pred, 0/88	NR	Bud, 2/88 Pred, 10/88	NR	Bud, 2/88 Pred, 6/88	Bud, 1/88 Pred, 3/88	Cortisol suppression greater with Pred (wk 8) ($P = .02$)	Rutgeerts et al, 1994 ²¹
NR	NR	NR	NR	NR	NR	NR	NR	Cortisol suppression greater with Pred ($P = .0035$)	Campieri et al, 1997 ²³
NR	NR	NR	NR	NR	NR	NR	NR	NR	Gross et al, 1996 ²²
NR	NR	Bud, 3/100 Prednisone, 2/101 ($P = NS$)	NR	Bud, 6/100 Prednisone, 6/101 ($P = NS$)	NR	Bud, 0/100 Prednisone, 2/101 ($P = NS$)	Bud, 2/100 Prednisone, 10/101 ($P < .05$)	NR	Bar-Meir et al, 1998 ¹³
NR	NR	1%	11%	7%		15%	1%		Entocort EC package insert ³¹⁴
NR	NR	0% 2% ($P = NS$) 1%	14% 7% NR	9% 6% 8%	NR	9% 11% 12%	3% 2% 1%	Abnormal cosyntropin stimulation test results found in corticosteroid-dependent patients on Pred compared with Bud ($P = .038$); ND between Bud and Pred in other groups	Schoon et al, 2005 ⁸⁰
		3% (NS)		13% (NS)		23% ^a ($P = .012$)	2% (NS)		
Prednisone, 13%	NR	Prednisone, 6%	Prednisone, 27%	NR	Prednisone, 6%	Prednisone, 17%	NR	NR	Summers et al (NCCDS), 1979 ^{36,73}
Placebo, 0% AZA, 0% Sulfa, 3% ($P < .05$ for prednisone)		Placebo, 0% AZA, 0% Sulfa, 3% ($P < .05$ for prednisone)	Placebo, 10% AZA, 5% Sulfa, 10% ($P < .05$ for prednisone)		Placebo, 0% AZA, 0% Sulfa, 3% ($P < .05$ for prednisone)	Placebo, 3% AZA, 5% Sulfa, 5% ($P < .05$ for prednisone)			
Prednisone, 13%	NR	Prednisone, 7%	Prednisone, 8%	NR	Prednisone, 6%	Prednisone, 16%	NR	NR	Summers et al (NCCDS), 1979 ^{36,73}
Placebo, 9% AZA, 4% Sulfa, 3% ($P = NS$)		Placebo, 0% AZA, 2% Sulfa, 3% ($P < .05$ for prednisone)	Placebo, 19% AZA, 17% Sulfa, 17% ($P = NS$)		Placebo, 0% AZA, 0% Sulfa, 3% ($P = NS$)	Placebo, 7% AZA, 6% Sulfa, 3% ($P < .05$ for prednisone)			

Table 4. (continued)

Type of IBD	n	Interventions tested	Time	Overall AEs	Corticosteroid-related side effects				
					Overall	Moon face	Acne	Hirsutism	Psychosis/ mood swings
CD	Total (sum of part 1/phase 2 + part 2)								
	113	Methylprednisolone 8 mg/day (from 48 mg/day)	2 y	Patients withdrawing due to AEs:	NR	Higher in Pred; incidence 1.9–2.5 per 100 patient months vs 0.49 for placebo	ND	ND	ND
	117			Pred, 5/113					
	112	Sulfa 3 g/day		Sulfa, 5/117					
	110	Methylprednisolone + 3 g/day Sulfasalazine		Combination, 6/112					
UC	N	Corticotropin (ACTH) 120 U/day	10 days	NR	Similar in both groups (specifics not provided)	NR	NR	NR	NR
	66	Hydrocortisone 300 mg/day IV		Placebo 3/110					

NOTE. Studies included provided toxicity data.

AE, adverse event; Bud, budesonide; ND, no difference; NR, not reported; BID, twice daily; Pred, prednisolone; SAE, serious adverse event; TID, 3 times daily; Sulfa, sulfasalazine.

*Significant.

mg/day, and then their dosage of prednisolone was tapered by 5 mg/wk until 20 mg and then 2.5 mg/wk until off the medication. Budesonide was superior to placebo in preventing a relapse. Patients taking budesonide had a 32% relapse rate at 13 weeks off corticosteroids, whereas 65% of patients who received placebo experienced a flare off corticosteroids ($P < .001$). A tapering range between 5 mg/wk and 10 mg every 10 days, slower below 20 mg/day, seems reasonable based on studies and anecdotal experience.

Adverse effects and special precautions. The beneficial effects of corticosteroids are counterbalanced by side effects that are frequently seen with their prolonged use (Table 4). Approximately 50% of all patients who use corticosteroids will experience adverse events.⁷³ Early adverse events include cosmetic side effects (such as acne, moon facies, and edema), sleep and mood disturbance, glucose intolerance, and dyspepsia. Side effects associated with prolonged use (usually >12 weeks of use but may occur in less time) include posterior sublentacular cataracts, osteoporosis and osteonecrosis of the femoral head, myopathy, and susceptibility to infections. In particular, patients on corticosteroids before elective IBD surgery have increased infectious complications compared with patients on immunomodulators.⁷⁴ Management of osteoporosis in the setting of IBD is the subject of another technical review.⁷⁵ In the majority of studies, there is an inverse relationship between use of corticosteroids and bone mineral density. Bone mineral density testing is recommended for patients on corticosteroids for >3 months. Other important risk factors include a

previous fracture and being postmenopausal. The use of bisphosphonates has been evaluated in a limited fashion in patients with CD and is effective in increasing bone mineral density.⁷⁶ Any patient with osteoporosis as defined by a T score ≤ 2.5 SDs below normal should be treated, and the most effective treatment is bisphosphonates. According to Bernstein et al, patients at low risk for corticosteroid-related fractures, such as premenopausal women and young men, do not need preventive treatment unless annual bone mineral density testing shows rapid bone loss.⁷⁵ Postmenopausal women or patients with previous fractures who are initiating or have been on corticosteroids for >3 months should take prophylactic bisphosphonate therapy. Both alendronate and risedronate are available in once-weekly preparations. Hormone replacement has been shown to be beneficial for prevention of bone loss,⁷⁷ but its use is controversial given the adverse events associated with hormone replacement therapy in postmenopausal women. Daily calcium (approximately 1200–1500 mg/day) and vitamin D (400–800 IU/day) should also be prescribed to patients with IBD receiving corticosteroid therapy. Osteonecrosis has been reported in patients with CD before initiation of corticosteroid therapy.⁷⁸ A recent study suggests that susceptibility to osteonecrosis is associated with carriage of a mutation in type II collagen.⁷⁹ There are also adverse events that occur with withdrawal of prednisone, including acute adrenal insufficiency (subsequent to sudden cessation of prednisone); a syndrome of myalgias, malaise, and arthralgias; or increased intracranial pressure.

Corticosteroid-related side effects									
Hypertension	Cataracts	Striae	Respiratory infection/sepsis	Ankle edema	Petechial bleeding	Easy bruising	Buffalo hump	Adrenocortical axis	References
ND	ND	ND	3 patients died of septic complications in Pred group	ND	NR	NR	NR	NR	Malchow et al, 1984 (ECCDS) ³⁷
NR	NR	NR	NR	ND	NR	NR	NR	Similar serum corticosteroid levels	Meyers et al, 1983 ⁴⁸

In studies comparing budesonide with prednisolone for the treatment of patients with ileocecal CD, budesonide is associated with fewer adverse events.²¹ Indeed, in short-term studies, budesonide is similar to placebo in its side effect profile.¹⁹ The most compelling safety data related to budesonide were shown in the European Matrix study, in which adverse effects and bone mineral density data were collected prospectively over 2 years in patients on maintenance budesonide 0–9 mg/day compared with prednisolone (Table 5).⁸⁰ Budesonide was not associated with a significant decrease in bone mineral density compared with baseline measurements. Patients who were corticosteroid naive at the time of entry had the largest decrease in bone mineral density when on prednisolone; significantly less bone loss occurred with budesonide (mean, -3.84% vs -1.04%, respectively; $P = .0084$). Based on these 2-year data, budesonide seems to be relatively safe for a select group of patients with ileocecal CD.

Any patient on long-term corticosteroid therapy is at risk for adrenal insufficiency when corticosteroids are tapered or discontinued. In particular, patients who have been receiving more than 30 mg/day of hydrocortisone or 7.5 mg/day of prednisolone for more than 3 weeks are susceptible to adrenal insufficiency, especially during a period of stress such as surgery.⁸¹ Signs of adrenal insufficiency include postural hypotension, nausea and vomiting, hyperkalemia, and hyponatremia. Cosyntropin stimulation tests are indicated for evaluation of these patients. Hydrocortisone replacement therapy is usually indicated in this situation because it provides mineralo-

corticoid activity to replace the aldosterone-related functions of the adrenals.

Recommendations for corticosteroid use. Mild to moderate IBD.

- Ileal-release preparations of budesonide (Entocort) are indicated for the treatment of patients with ileal and right-sided colonic CD. Ileal-release preparations of budesonide are not effective in patients with UC. (Grade A)
- The use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate to severe disease who failed to respond to first-line therapies for IBD such as mesalamine (UC) or budesonide (CD). (Grade B)
- Topical therapy with either hydrocortisone (Grade A) or budesonide (Grade B) is effective for distal colonic inflammation.

Moderate to severe IBD.

- Corticosteroids such as prednisone are effective in both patients with CD and patients with UC. (Grade A)
- Corticosteroids are not effective for the treatment of patients with perianal fistulas. (Grade C)

Severe and fulminant IBD.

- Hospitalization for parenteral corticosteroids is indicated for patients failing to respond to oral corti-

Table 5. Changes in Bone Mineral Density in Budesonide-Treated Versus Prednisolone-Treated Patients With CD⁸⁰

Patient characteristic	Change in bone mineral density at the end of 2 years (mean % change)	New fractures
Corticosteroid naive (n = 98)	Budesonide, -1.04 Prednisolone, -3.84 (<i>P</i> = .0084)	Overall: 1 new in prednisolone 1 worsened in patient treated with budesonide
Corticosteroid exposed in the past (n = 83)	Budesonide, -1.66 Prednisolone, -0.15 (<i>P</i> = .11)	
Corticosteroid dependent (n = 90)	Budesonide, 0.17 Prednisolone, 0.49 (<i>P</i> = .76)	

NOTE. Patients who were corticosteroid free at the beginning of the study were randomized to prednisolone 40 mg/day or budesonide 9 mg/day. Patients who were corticosteroid dependent were randomized to continue their current dosage of prednisolone or switch to budesonide 9 mg/day. Tapering was accomplished by lowering the dosage of prednisolone by 5 mg/wk. Treatment with corticosteroids was reinitiated or the dosage increased for return of symptoms. The mean dosage of budesonide was 6.8 mg/day, and the mean dosage of prednisolone was 14.9 mg/day.

corticosteroids or for patients with severe disease with UC (Grade A) or CD (Grade B).

Maintenance therapy.

- Conventional corticosteroids are not efficacious in maintenance treatment of patients with CD (Grade A) or patients with UC (Grade B).
- Budesonide therapy is effective in the maintenance of short-term (3 months) but not long-term (1 year) remission compared with placebo in patients with mild to moderate ileocecal CD. (Grade A)

Dosing and tapering for IBD.

- Dosages in the range of 40–60 mg/day or 1 mg · kg⁻¹ · day⁻¹ of prednisone or equivalent are effective for induction of remission. (Grade A)
- Induction of response averages 7–14 days. A gradual taper by 5 mg/wk of prednisone (or equivalent corticosteroid) to a dose of 20 mg and then 2.5–5 mg/wk below 20 mg is recommended. (Grade B)
- Budesonide may be tapered gradually from the initial induction dose of 9 mg to doses of 6 mg and subsequently 3 mg. Budesonide does suppress the adrenocortical axis; clinicians should evaluate for adrenal insufficiency as warranted by clinical symptoms. (Grade C)
- An inability to taper corticosteroids is an indication for antimetabolite and/or infliximab therapy (see following text). (Grade A)
- For patients failing to respond to 7–14 days of high-dose oral prednisone or equivalent corticosteroid therapy, parenteral corticosteroids are indicated. (Grade C)

- Dosages for parenteral corticosteroids typically are in the range of methylprednisolone 40–60 mg/day or hydrocortisone 200–300 mg/day. (Grade A)

Monitoring for complications.

- Periodic bone mineral density assessment is recommended for patients on long-term corticosteroid therapy (>3 months).⁷⁵ (Grade A)
- Annual ophthalmologic examinations are recommended for patients on long-term corticosteroid therapy. (Grade C)
- Patients with corticosteroid use within the past year are at greater risk for adrenal insufficiency, especially following surgery, and may need stress-dose corticosteroids perioperatively. (Grade C)
- Patients should be monitored for glucose intolerance and other metabolic abnormalities. (Grade B)
- Patients being treated with corticosteroids are at increased risk for infectious complications. (Grade B)

AZA and 6-MP

AZA and 6-MP are related immunomodulators that are perceived to act through metabolites, 6-thioguanine nucleotides (6-TGN), by mechanisms that remain unclear. Their onset of full activity is slow and may take 3 months. These drugs are members of the thiopurine class of medications and are commonly used to treat patients with CD and UC who are corticosteroid dependent in an attempt to withdraw corticosteroids and maintain patients in remission off corticosteroids.

Pharmacology. 6-MP and the nitroimidazole derivative of 6-MP, AZA (its prodrug), are thiopurine

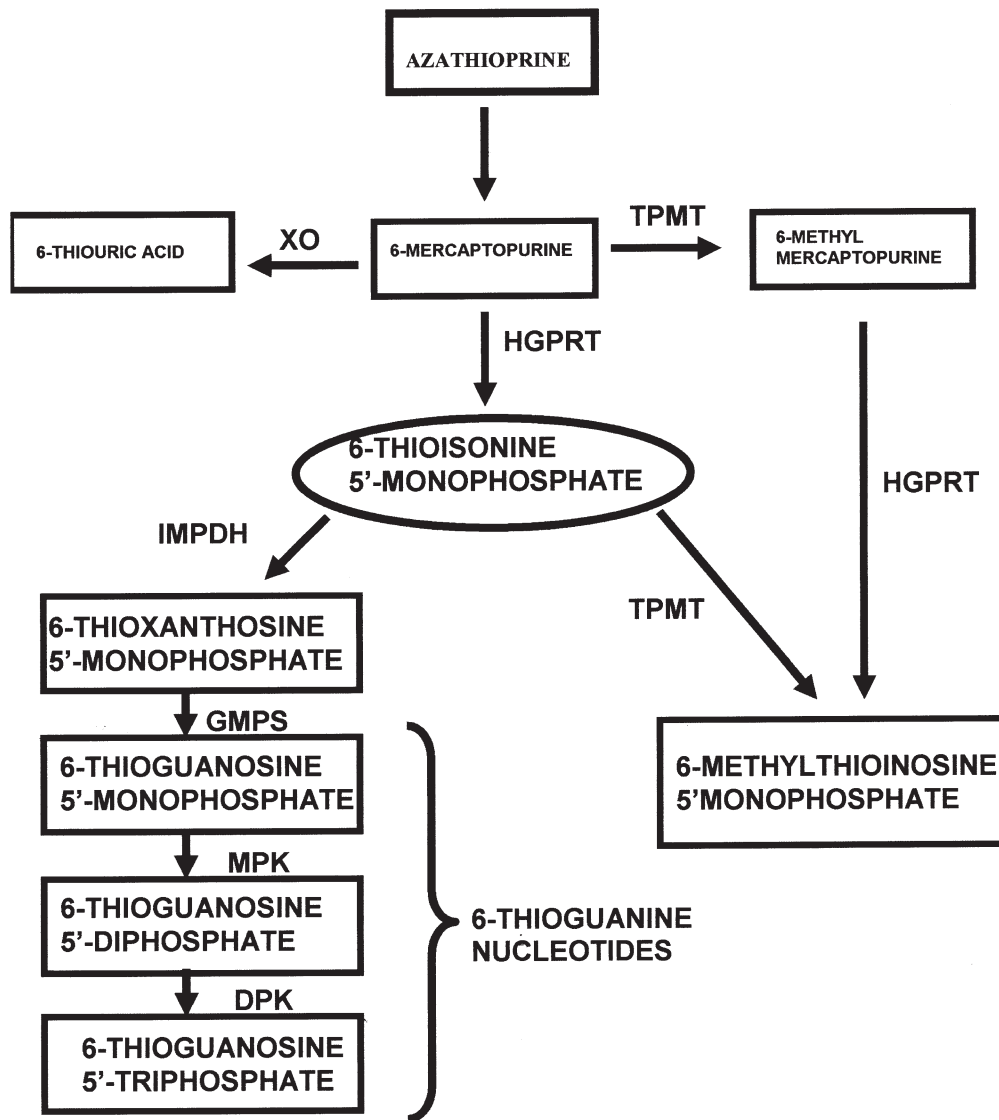


Figure 1. Pathway involved with AZA and 6-MP metabolism. HG-PRT, hypoxanthine guanine phosphoribosyl transferase; IMPDH, inosine monophosphate dehydrogenase; XO, xanthine oxidase; GMPS, guanine monophosphate synthetase; MPK, monophosphate kinase; DPK, diphosphate kinase.

analogues. AZA is metabolized to 6-MP. 6-MP is metabolized to 6-thioisonine 5'-monophosphate by the enzyme hypoxanthine phosphoribosyl transferase. 6-Thioisonine 5'-monophosphate is eventually metabolized to 6-TGN, the active metabolites causing inhibition of DNA and RNA synthesis and likely T-cell apoptosis (Figure 1).⁸² 6-MP is also metabolized to 6-methylmercaptopyrurine (6-MMP) by the enzyme thiopyrurine methyltransferase (TPMT) and 6-thiouric acid by the enzyme xanthine oxidase. Both 6-thiouric acid and 6-MMP are inactive metabolites of 6-MP. The 3 enzymes metabolizing 6-MP are in constant competition for substrate, and the concentration of the metabolites of 6-MP is based on the concentrations of these enzymes. A total of 84% of 6-MP is quickly metabolized by xanthine oxidase found in high concentrations in enterocytes and hepatocytes, leaving only 16% left to be catabolized by TPMT and hypoxanthine phosphoribosyl transferase.⁸³

Some,^{84,85} but not all,^{86,87} recent retrospective studies have suggested that measurement of AZA and 6-MP metabolites may be useful in dose adjustments. It has been suggested that serum 6-TGN levels of greater than 235 pmol/8 × 10⁸ erythrocytes may be associated with a greater response rate than in patients with lower 6-TGN levels. The positive and negative predictive values can vary substantially, with positive predictive values ranging from 17% to 86% and negative predictive values ranging from 35% to 100%.⁸⁸ Some investigators have also suggested that hepatotoxicity may correlate with the elevated levels of 6-MMP.⁸⁴ However, hepatotoxicity has not been demonstrated in patients with normal liver-associated chemistries and elevated 6-MMP levels; hence, continued therapy with AZA/6-MP is advocated in these circumstances. Additionally, a recent retrospective study⁸⁹ suggested that a small subset of patients with 6-TGN levels of less than 235 pmol/8 × 10⁸ erythro-

cytes may remain refractory to increasing doses of 6-MP/AZA because they may preferentially metabolize 6-MP/AZA to 6-MMP and maintain low 6-TGN levels.⁸⁹ Given the conflicting data, the retrospective nature of these studies, and the limited positive and negative predictive values for these particular uses, the utility of these tests needs prospective controlled evaluation before their routine use can be recommended. The utility of these metabolite markers, however, can assist an individual in determining whether a patient is noncompliant with their immunomodulator therapy.

6-MP and its prodrug AZA are both metabolized by TPMT, an enzyme that exhibits variation as a result of a genetic polymorphism of its alleles. This enzyme can now be measured by commercial laboratories. Approximately 0.3% of the general population has low to absent enzyme activity, 11% has intermediate levels, and 89% has normal to high levels of activity.⁹⁰ However, only about one fourth of cases of leukopenia in practice are associated with the presence of one of these genetic polymorphisms.⁹¹ Prospective studies evaluating dose optimization based on measurements of TPMT, 6-TGN, or 6-MP levels to monitor clinical response are still lacking. It remains uncertain whether this strategy provides substantial incremental benefit to the traditional routine of monitoring complete blood count, liver-associated laboratory chemistries, and clinical response. Despite the lack of such data, routine use of TPMT genotype or enzyme activity is currently recommended by the Food and Drug Administration (FDA) before initiation of therapy with either AZA or 6-MP.⁹²

Drug interactions and toxicity. The major concern on the short-term side effects of 6-MP and AZA is bone marrow suppression, occurring in 2%–5% of patients treated with these agents.^{93,94} This effect is dose related and is managed with dose reduction or withdrawal of the drug. Leukopenia is the most common presentation of this hematologic effect. In a study of 739 patients treated with AZA for IBD,⁹³ leukopenia (defined as a white blood cell count $<3.0 \times 10^9/L$) occurred in 28 patients (3.8%), while thrombocytopenia (defined as a platelet count $<100,000 \times 10^6/L$) occurred in 15 patients. Nine patients developed isolated thrombocytopenia without leukopenia, and 3 developed pancytopenia. In that study, myelotoxicity from AZA developed at any time during treatment, ranging from 2 weeks to 11 years after starting the medications. Routine monitoring of blood count is recommended. Some recommend obtaining a complete blood count weekly for 4 weeks, biweekly for 4 weeks, and then every 1–2 months for the duration a patient is treated with AZA or 6-MP.⁹⁵ The frequency that mon-

itoring needs to be performed has not been formally tested.

Pancreatitis has been reported to occur in 1.3%–3.3% of patients treated with AZA or 6-MP for IBD.^{94,96} The effect is dose independent and typically occurs within the first 3–4 weeks of initiating therapy. The pancreatitis usually resolves when the drug is discontinued; persistent pancreatitis justifies an evaluation for another etiology. Recurrent pancreatitis almost universally develops upon rechallenge with either drug. Other gastrointestinal-related side effects, including nausea, vomiting, and abdominal pain, are common but usually mild. They often occur early and improve with dose reduction or over time. Nonspecific reactions, including fever, rash, and arthralgia, are usually dose independent and respond to withdrawal of the drug.^{94,97} Recurrence of similar reactions often occurs with rechallenge to the same medication. However, there may be individuals who develop allergic reactions with 6-MP and are able to tolerate subsequent administration with AZA⁹⁸ and vice versa.⁹⁹ Liver disease has also been implicated to result from therapy with AZA or 6-MP. Hepatotoxicity is a rare complication, and the exact type of hepatic injury is unknown. Possibilities include drug-induced hepatitis, cholestasis, nodular regenerative hyperplasia, and peliosis.⁹⁷

Various infectious complications have been reported, including disseminated cytomegalovirus infection, liver abscess, pneumonia, *Listeria* cerebritis, herpes zoster, septic phlebitis with arthritis, viral hepatitis, Q fever, and cytomegalovirus colitis.^{94,100–102} Many of these occurred in the absence of leukopenia. It has yet to be analyzed in a prospective randomized fashion if the presence of leukopenia leads to a higher rate of infectious complications. A recent study, however, was performed suggesting that preoperative use of AZA or 6-MP for elective bowel surgery in itself is not associated with a significant increase in postoperative infectious complications; rather, it is when this is combined with corticosteroids that this risk is augmented substantially.⁷⁴

Combining studies of nearly 1000 patients, the overall incidence of adverse events reported was 15%, and 10% of patients experienced significant adverse events requiring withdrawal from the studies (Table 6). There was, however, only 1 report of death directly attributable to 6-MP therapy. In the meta-analysis of Pearson et al,¹⁰³ the pooled OR for experiencing an adverse event requiring withdrawal of AZA or 6-MP therapy was 5.26 (confidence interval [CI], 2.20–12.60) compared with placebo.

Several categories of drugs have been shown to interact with 6-MP and AZA metabolism and include medica-

Table 6. Short-term Adverse Events Reported in Controlled and Large Uncontrolled Studies

References	Allergic reactions	Bone marrow suppression	Pancreatitis	Hepatitis	Infections	Gastrointestinal symptoms not due to pancreatitis (nausea, abdominal discomfort, diarrhea)	Others/not specified	Malignancy	Total no.
Controlled studies with AZA									
Willoughby et al, 1971 ¹²⁰	0	0	0	0	0	0	0	0	0
Rhodes et al, 1971 ¹¹⁹	1	0	0	0	0	0	0	0	1
Klein et al, 1974 ¹²¹	2	0	0	0	0	0	0	0	2
Mantzaris et al, 2004 ¹³²	5 (5 rash)	6 (6 leukopenia)	1	1	26 respiratory 1 urinary 3 other	4 diarrhea 2 abdominal pain	1 paresthesia 17 minor events	0	63
Rosenberg et al, 1975 ¹³⁸	0	0	0	0	0	1	0	0	1
O'Donoghue et al, 1978 ¹³⁹	0	1 (pancytopenia)	0	0	0	0	0	0	1 ^a
Summers et al, 1979 ³⁶	1	2 (2 leukopenia)	3	0	0	1	4	0	11
Ewe et al, 1993 ¹²³	0	0	0	0	0	1	0	0	1
Candy et al, 1995 ¹²⁴	0	0	0	0	0	0	0	0	0
Jewell and Truelove, 1974 ¹²⁷	1	1 (leukopenia)	0	0	0	1	0	0	3
Rosenberg et al, 1975 ¹²⁸	0	0	0	0	0	0	0	0	0
Caprilli et al, 1975 ¹³⁰	0	1 (leukopenia)	0	0	0	0	3	0	4
Kirk and Lennard-Jones, 1982 ¹²⁹	0	0	0	0	0	7	0	0	7
Hawthorne et al, 1992 ¹²⁶	0	2 (1 leukopenia, 1 thrombocytopenia)	0	0	0	0	0	0	2
Controlled studies with 6-MP									
Present et al, 1980 ¹²²	2	2 (2 leukopenia)	1	0	1	1	3	0	10
Hanauer et al, 2004 ¹⁴⁶	0	2 (2 leukopenia)	0	0	0	2 diarrhea 1 flatus 1 gastrointestinal bleed	2 alopecia 1 phlebitis	0	9
Markowitz et al, 2000 ¹³⁷	0	6 (6 leukopenia)	0	4	0	0	0	0	10
Oren et al, 1997 ¹²⁵	0	1 leukopenia and stomatitis	0	0	0	0	0	0	1
Uncontrolled study, 6-MP									
Present et al, 1989 ⁹⁴	8	8	13	1	29	1	0	12 ^b	60
Uncontrolled study, AZA or 6-MP									
Bouhnik et al, 1996 ³¹⁵	0	24 (22 leukopenia, 2 thrombocytopenia)	0	4	4	0	0	4 ^c	26
Total no.	18	56	18	14	60	21	21	16	212

^aOne death from sepsis in the setting of pancytopenia.
^bOnly 1 diffuse histiocytic lymphoma of brain may be associated with 6-MP.
^cTwo skin cancer, 1 renal cell adenocarcinoma, 1 brain lymphoma.

tions that have 5-aminosalicylates as the active moiety (sulfasalazine, mesalamine, olsalazine, and balsalazide), allopurinol, aspirin, and furosemide. In a study by Lowry et al, red blood cell 6-TGN levels were slightly higher but not statistically significant in subjects taking mesalamine, sulfasalazine, or olsalazine concurrently compared with subjects not taking these medications (182 vs

153 pmol/8 × 10⁸, respectively; P = .10).¹⁰⁴ The pathway of the drug interaction between 6-MP/AZA and 5-aminosalicylates is believed to be by inhibition of the TPMT enzyme.^{103–107} Allopurinol inhibits xanthine oxidase, leading to 6-MP/AZA toxicity.¹⁰⁴ Subjects on these medications should be more carefully monitored for myelosuppression.

Despite the growing evidence of the safety of these immunomodulators for patients with IBD, fear of developing lymphoma remains one of the most common concerns among both patients and physicians in deciding whether or not to use these medications.¹⁰⁸ Recently, a decision analysis using a Markov model¹⁰⁹ to determine the impact of AZA therapy on survival and quality-adjusted life expectancy was published. In the model, treatment with AZA of patients with CD with a corticosteroid-induced remission resulted in an average increase in life expectancy of 0.04 years and 0.05 quality-adjusted years. This is comparable to use of the measles or hepatitis B vaccines and the use of ticlopidine in patients at high risk for stroke. Furthermore, the study also showed that this incremental gain in life expectancy decreased with increasing patient age and increasing risk of lymphoma, thus conferring the greatest increase with therapy in young patients who have the lowest baseline risk of lymphoma and the greatest life expectancy. Recently, a meta-analysis of 6 studies revealed an increased risk of lymphoma in patients with IBD treated with 6-MP or AZA. They observed 11 lymphomas versus an expected number of 2.71 and concluded that 6-MP/AZA use was associated with a 4-fold increase in the incidence of lymphoma in patients with IBD.¹¹⁰

Dosing, onset of action, and duration of therapy.

Based on the reported clinical trials, the most effective doses appear to be AZA 2.0–3.0 mg/kg and 6-MP 1.0–1.5 mg/kg, although there has not yet been a head-to-head comparison at various dose levels or a comparative trial evaluating the efficacy of 6-MP versus AZA in patients with IBD. In addition, it has not yet been well determined how best to start therapy: dose escalating to the weight-based dose versus starting immediately at the weight-calculated dose. If a dose-escalating method is chosen, AZA may be started at 50 mg daily and the dose increased by 25 mg every 1–2 weeks to a target dose of 2.0–3.0 mg/kg along with monitoring for leukopenia and other potential adverse events. A similar approach can be assumed with use of 6-MP. If a dose-escalating method is chosen, 6-MP may be started at 50 mg daily and the dose increased by 25 mg every 1–2 weeks to a target dose of 1.0–1.5 mg/kg along with similar monitoring for leukopenia and other potential adverse events. If starting immediately at the weight-calculated dose (AZA 2.0–3.0 mg · kg⁻¹ · day⁻¹ and 6-MP 1.0–1.5 mg · kg⁻¹ · day⁻¹), it has been recommended by some investigators to assess for TPMT genotype or phenotype, although this approach has not been studied in a comparative fashion with the approach of a gradual escalation of dose. It has recently been shown to be cost-effective to measure TPMT enzyme activity before initiation of therapy with AZA or 6-MP.¹¹¹ It is advised that subjects who

are heterozygous for the TPMT mutation or intermediate enzyme activity should start 6-MP and AZA at a reduced dose, although their risk of myelosuppression is not clearly increased when compared with those with normal TPMT enzyme activity.⁸² Some studies suggest that individuals with intermediate enzyme activity (or individuals who are heterozygous for TPMT) are more likely to have either a higher probability of developing leukopenia or a shorter time to onset of leukopenia,¹¹² whereas others have not suggested similar findings.^{84,86,91,113–115}

Until more studies are performed, formal evidence-based recommendations to vary treatment (eg, maximal dose used or rapidity of achieving maximal dose) based on whether an individual has the wild type (full TPMT enzyme activity) or intermediate TPMT enzyme activity cannot be formally established.

Thus, TPMT phenotype should be assessed before initiation of therapy with AZA or 6-MP in an effort to detect individuals who have low enzyme activity (those who are homozygous deficient in TPMT) in an effort to avert adverse events. At present, there is insufficient evidence to recommend changing the dose for those who are heterozygous for TPMT (those with intermediate enzyme activity).⁸² It is recommended that subjects who are homozygous for the TPMT mutation should be placed on other forms of therapy due to the high risk of myelosuppression. A recent case series suggests that it may be possible to safely use AZA or 6-MP in this situation.¹¹⁶ In this study, patients with IBD receiving AZA with myelosuppression who were homozygous for the TPMT mutation also had 6-TGN levels measured. The dose of AZA was titrated down until the 6-TGN level was reduced and leukopenia ceased. If treatment with AZA or 6-MP is continued in this situation, a highly vigilant approach should be taken.

AZA and 6-MP have a significantly delayed onset of action. Several studies have shown clinical benefit begins to occur after 2–3 months of treatment.¹¹⁷ The best approach if rapid clinical response is needed is to start on another form of therapy such as corticosteroids until the period of clinical onset of AZA or 6-MP has had adequate time to begin.

Treatment of active disease. *Active CD.* Brooke et al in 1969¹¹⁸ first reported successful treatment with AZA in 6 patients with CD previously refractory to standard therapy. Since then, there have been many reports in the literature using these agents in patients with CD. There have been 8 randomized controlled trials evaluating the utility of 6-MP or AZA in patients with active CD^{36,119–125} (Table 7). Two of the 8 studies showed a significant response compared with placebo.

Table 7. Results of Controlled Trials of AZA/6-MP for CD

References	Indication for treatment	Total no. of patients	Drug dose	Concurrent corticosteroid therapy	Treatment duration	Response in treatment group (%)	Response in placebo group (%)	Response (P value)
Induction therapy								
Willoughby ¹²⁰	Disease exacerbation; none on steroid	12	Azathioprine 2.0 ^a	All received steroid	6 mo	100	17	NR
Rhodes ¹¹⁹	Active disease; fistulous disease; 2 on steroid, 3 on sulfasalazine	16	Azathioprine 2.0 ^b	Pre-study steroid or sulfasalazine continued; steroid added to therapy in 1 patient	2 mo	0	0	NS
Klein ¹²¹	Active disease refractory to other medical therapy; fistula; unknown steroid use	26	Azathioprine 3.0	Concurrent steroid use at discretion of treating physician	4 mo	46	46	NS
Ewe et al, 1993 ¹²³	Active disease, CDAI score >150	42	AZA 2.5 mg · kg ⁻¹ · day ⁻¹	All received corticosteroid taper	4 mo	76	38	.03
Candy et al, 1995 ¹²⁴	Part I: active disease, CDAI score >200	63	AZA 2.5 mg · kg ⁻¹ · day ⁻¹	All received corticosteroid taper	3 mo	76	67	.6
Oren et al, 1997 ¹²⁵	Chronic active disease, Harvey-Bradshaw index ≥7; 57 patients on mesalamine, 65 on corticosteroid	84 ^c	6-MP 50 mg/day	Continued at discretion of treating physician	9 mo	41	46	NS ^d
Summers et al, 1979 ³⁶	Part I, phase 1: active disease, CDAI score 150–450; none on corticosteroid	136	AZA 2.5 mg · kg ⁻¹ · day ⁻¹	None	17 wk	36	26	.25
Present et al, 1980 ¹²²	Chronic active disease; fistulous disease; 53 patients on corticosteroid, 39 on sulfasalazine	72	6-MP 1.5 mg · kg ⁻¹ · day ⁻¹	Adjusted at the discretion of treating physician	12 mo	72	14	<.001
Maintenance therapy								
Willoughby et al, 1971 ¹²⁰	Stable symptoms, all corticosteroid dependent	10	AZA 2.0 mg · kg ⁻¹ · day ⁻¹	Corticosteroid taper after 4 wk of treatment	6 mo	80	40	NR
Rosenberg et al, 1975 ¹³⁸	Stable disease; all corticosteroid dependent	20	AZA 2.0 mg · kg ⁻¹ · day ⁻¹	Corticosteroid taper	6 mo	70	40	<.05
O'Donoghue et al, 1978 ¹³⁹	Remission; 15 patients on corticosteroid, sulfasalazine, or both	51	AZA 2.0 mg · kg ⁻¹ · day ⁻¹	Corticosteroid/sulfasalazine continued at prestudy dose	12 mo	54	30	<.05
Summers et al, 1979 ³⁶	Part I, phase 2: remission from phase 1, CDAI score <150	39	AZA 2.5 mg · kg ⁻¹ · day ⁻¹	NR	35 wk	84	75	NS
Candy et al, 1995 ¹²⁴	Part II: remission CDAI score <150	155	AZA 1.0 mg · kg ⁻¹ · day ⁻¹	NR	52 wk	69	64	.53
Hanauer et al, 2004 ¹⁴⁶	Postoperative maintenance	47 6-MP, 40 placebo, 44 mesalamine	6-MP 50 mg daily	No corticosteroids	24 mo	Clinical recurrence, 6-MP, 50% at 2 y; endoscopic recurrence, 43% at 2 y	Clinical recurrence, 77% at 2 y; endoscopic recurrence, 64% at 2 y	6-MP vs placebo: clinical and endoscopic recurrence at 2 y (P < .05) .007
Markowitz et al, 2000 ¹³⁷	Maintenance of remission	55 total children: 27 6-MP, 28 controls	6-MP 1.5 mg · kg ⁻¹ · day ⁻¹	All given corticosteroids with a taper	18 mo	89% initial remission, then 18 mo later 9% of these experienced a relapse	89% initial remission, then 18 mo later 47% of these experienced a relapse	

Modified and reproduced with permission from Su C, Stein R, Lewis JD, Lichtenstein GR. Azathioprine or 6-mercaptopurine for inflammatory bowel disease: do risks outweigh benefits? *Dig Liver Dis* 2000;32:518–531.

NR, not reported.

^aAZA 4.0 mg · kg⁻¹ · day⁻¹ for 10 days for acute exacerbation.

^bAZA 4.0 mg · kg⁻¹ · day⁻¹ for 10 days then 2.0 mg · kg⁻¹ · day⁻¹ for 6.5 weeks.

^cThree-arm study comparing 6-MP, methotrexate, and placebo.

^dNS compared with both placebo and methotrexate.

Table 8. Results of Controlled Trials of AZA/6-MP for UC

References	Indication for treatment	Total no. of patients	Drug dose	Concurrent corticosteroid therapy	Treatment duration	Response in treatment group (%)	Response in placebo group (%)	Response (<i>P</i> value)
Induction therapy								
Ardizzone et al, 2001 ¹³¹	Corticosteroid-dependent active disease	52 (27 AZA, 25 mesalamine)	AZA 2.0 mg/kg daily (compared with mesalamine 3.2 g/day)	Required ≥ 10 mg of prednisone for prior 6 months; with 2 attempted tapers; all placed on prednisolone 40 mg daily	6 mo	Clinical and endoscopic remission and corticosteroid withdrawal: 58	Clinical and endoscopic remission and corticosteroid withdrawal: 26	.042
Jewell and Truelove, 1974 ¹²⁷	Active disease	80	AZA 2.5 mg \cdot kg ⁻¹ \cdot day ⁻¹	All receiving corticosteroid	1 mo	78	68	NS
Caprilli et al, 1975 ¹³⁰	Acute disease	20	AZA 2.5 mg \cdot kg ⁻¹ \cdot day ⁻¹	None	3 mo	60	80 ^a	NS
Kirk and Lennard-Jones, 1982 ¹²⁹	Chronic active disease; unknown corticosteroid use	44	AZA 2.0–2.5 mg \cdot kg ⁻¹ \cdot day ⁻¹	Concurrent therapy at discretion of treating physician	6 mo	NR	NR	<.001
Maintenance therapy								
Jewell and Truelove, 1974 ¹²⁷	Remission	80	AZA 1.5–2.5 mg \cdot kg ⁻¹ \cdot day ⁻¹	NR	11 mo	40	23	.18
Rosenberg et al, 1975 ¹²⁸	Chronic UC, all corticosteroid dependent	30	AZA 1.5 mg \cdot kg ⁻¹ \cdot day ⁻¹	Corticosteroid dose adjusted at the discretion of an independent physician	6 mo	NR	NR	<.05
Hawthorne et al, 1992 ¹²⁶	Group I: remission; none on corticosteroid, 55 patients on mesalamine	67	AZA 100 mg/day (mean)	Concurrent therapy continued at discretion of treating physician	12 mo	64	41	.04
	Group II: chronic stable low-grade disease or corticosteroid-dependent disease; 6 patients on corticosteroid, 11 on mesalamine	12	AZA 100 mg/day (mean)	Concurrent therapy continued at discretion of treating physician	12 mo	29	60	NS
Mantzaris et al, 2004 ¹³²	Remission maintenance in corticosteroid-dependent UC	70 total patients: 34 AZA, 36 AZA/olsalazine	AZA 2.2 mg/kg daily	All on corticosteroids	2 y	18% relapse after 2 y in AZA + olsalazine group	19% relapse after 2 y in AZA alone group	NS
Sood et al, 2000 ¹³³	Remission maintenance in severely active UC	83	AZA 2.0 mg/kg daily	All on corticosteroids (prednisone at 1 mg/kg) and sulfasalazine 6–8 g/day	1 y	NR	NR	NS

NR, not reported.

^aTreated with sulfasalazine, not placebo.

Active UC. The data on the utility of AZA or 6-MP therapy for UC is less clear than that for CD. To date, there have been 8 controlled trials evaluating the effectiveness of AZA for the treatment of active UC^{126–133} (Table 8). Optimal dosing for the treatment of UC has not been determined. The studies thus far evaluating patient response to treatment with AZA have ranged in dose from 1.5 to 2.5 mg/kg. The heterogeneity in trial design in particular focusing on dosing and end point (achieving remission vs achieving corticosteroid withdrawal) has made it difficult to adequately interpret the available data. In addition, the use of pharmacogenomics has not been adequately applied to UC. Future prospective studies with measurement of dose optimization based on clinical efficacy and remission compared with measurements of TPMT, 6-TGN, and 6-MMP levels are still needed to better define appropriate treatment algorithms and doses in patients with UC. These particular studies can also assess the level (if any is present) of incremental benefit to the traditional routine of monitoring complete blood count, liver-associated laboratory chemistries, and clinical response. Given the aforementioned inadequacies, it seems prudent to treat patients with a dosage of AZA up to 3.0 mg/kg daily.

No controlled trial of 6-MP for UC has been performed, and no study has been performed that compared the efficacy of 6-MP with AZA in patients with UC. Despite the widespread acceptance of AZA/6-MP for the treatment of patients with UC, especially those with corticosteroid-dependent disease, there remains limited evidence-based data to support their overall efficacy in this disorder or to delineate a dose-response effect in UC. Additionally, as in the case with CD, studies using AZA for inducing remission of UC reported conflicting results and were less convincing than that for maintaining remission. The clinical trials evaluating AZA in the early 1970s provided equivocal results regarding the efficacy of AZA in patients with UC; however, corticosteroid-sparing effects were suggested.^{126,128,129,131,132} Two early double-blind, randomized, placebo-controlled trials evaluating AZA as an induction therapy for the treatment of patients with active UC reported conflicting results.^{127,130} The first study of 1-month duration failed to show the benefit of AZA therapy for inducing remission compared with placebo.¹²⁷ In the second study of 3-month duration, AZA 2.5 mg · kg⁻¹ · day⁻¹ was shown to be modestly beneficial in the treatment of maintenance of remission and corticosteroid sparing for UC; maintenance efficacy was believed to be no better than that of sulfasalazine in this study.¹³⁰

Two randomized controlled studies have shown no benefit of AZA (2.5 mg · kg⁻¹ · day⁻¹) for the treatment

of patients with active UC, whereas 1 study showed more significant decreased disease activity compared with placebo ($P < .001$). An early study with AZA (1.5–2.5 mg · kg⁻¹ · day⁻¹) failed to show an effect of AZA in preventing relapse at 12 months of treatment.¹²⁷ In 1 controlled trial assessing the efficacy of AZA for maintenance therapy, patients with UC who had achieved remission for at least 2 months on a median of 100 mg/day of AZA were randomized to receive continued active therapy versus placebo.¹²⁶ Those who continued treatment with AZA had a 1-year relapse rate of 36%, compared with 59% in those converted to placebo ($P = .04$), suggesting continued efficacy of AZA as maintenance therapy for UC in patients who have already shown a response to the drug. A therapeutic efficacy for preventing relapse was also reported in several series of patients in remission induced by IV cyclosporine for corticosteroid-refractory severe UC and who were maintained on AZA (2.0–2.5 mg · kg⁻¹ · day⁻¹).^{134–136}

Corticosteroid-refractory and corticosteroid-dependent CD. Controlled and uncontrolled trials of AZA in dosages up to 1.5–2.5 mg · kg⁻¹ · day⁻¹ have shown its effectiveness in patients with CD who do not respond to or cannot be weaned from corticosteroids.^{120–124} Uncontrolled series have also demonstrated its value in achieving remission in patients who are refractory to high doses of oral corticosteroids.

Corticosteroid-sparing effect in UC. There have been several studies showing a significant corticosteroid-sparing response with a dosage of AZA ranging from 1.5 mg to 2.5 mg · kg⁻¹ · day⁻¹ for 6 months, although the effect seems to wane with longer follow-up.^{128,129,131}

Maintenance of quiescent CD. There have been 7 randomized controlled trials evaluating the effectiveness of 6-MP or AZA in patients with quiescent CD.^{120,123,124,137–139} (Table 7). In 3 of the studies, patients were corticosteroid dependent or had a corticosteroid-induced remission. All 3 studies showed significant maintenance of remission compared with the placebo group. There were 4 studies in a cohort of patients with AZA-induced remission, with 2 studies showing significant response compared with placebo. Even the studies not showing a significant difference compared with placebo still had a higher response compared with placebo.

Overall, the data are favorable for using AZA in patients with CD. A meta-analysis of randomized controlled trials from 1966 to 1994 of AZA and 6-MP in active and quiescent CD was completed by Pearson et al.¹⁰³ The OR for a clinical response in active CD was 3.09 (95% CI, 2.45–3.91); this decreased to 1.45 (95% CI, 1.12–1.87) when excluding the single clinical trial using 6-MP. For quiescent CD, the OR for maintaining

remission if on AZA was 2.27 (95% CI, 1.76–2.93). There were no trials of 6-MP for maintaining remission in CD at the time of the meta-analysis. Both longer duration and higher dose of AZA/6-MP were associated with improved response, and a corticosteroid-sparing effect was seen in subjects with active and quiescent disease.

Maintenance of quiescent UC. The immunomodulators AZA and 6-MP have also been studied for prevention of relapse in patients with UC. As with induction of remission in patients with UC, there have been no studies comparing 6-MP with AZA. In patients whose remission was achieved with AZA, continuation of active drug reduced the 12-month relapse rate to 36% compared with 59% on placebo.¹²⁶ There have been 2 randomized placebo-controlled studies of AZA (1.5–2.5 mg · kg⁻¹ · day⁻¹ and 100 mg/day mean dose) for the maintenance of remission in patients with UC, both suggesting a benefit.^{126,127} Hawthorne et al showed a significant difference in maintenance of remission in the AZA group compared with placebo in a cohort of patients who had already shown a response to the drug (64% vs 41%, respectively; hazard rate ratio, 0.5; 95% CI, 0.25–1.0) after 1 year. In a subgroup of patients in that study who had been treated with AZA for a minimum of 6 months before the trial, 69% receiving AZA versus 39% receiving placebo maintained remission after 1 year ($P < .01$).¹²⁶ A study by Jewell et al showed a trend for better response in the AZA group compared with placebo (40% vs 23%), but this was not statistically significant ($P = .18$).¹²⁷ Another placebo-controlled trial was performed assessing maintenance of remission in patients with severe UC.¹³³ The study was a 1-year, randomized, placebo-controlled trial. A total of 83 patients with severe UC were enrolled. Fifty patients who experienced a relapse within 2 months on corticosteroid withdrawal were randomized into 2 groups. The AZA group received oral sulfasalazine (6–8 g/day), oral prednisolone (1 mg · kg⁻¹ · day⁻¹), and oral AZA (2 mg · kg⁻¹ · day⁻¹). The placebo group received oral sulfasalazine (6–8 g/day), oral prednisolone (1 mg · kg⁻¹ · day⁻¹), and placebo. Corticosteroids were tapered over 12–16 weeks. Five patients (2 in the AZA group and 3 in the placebo group) dropped out of the study. Three patients in the AZA group experienced side effects. The number of patients going into complete remission and partial remission was not significantly different between the 2 groups. The proportion of relapses in the AZA group was lower than in the placebo group ($P < .05$). The conclusion of the study was that in patients with UC, AZA had no effect in achieving re-

mission when given in combination with prednisolone; however, it decreased the proportion of relapses.

A recent study was performed assessing if AZA (2.2 mg/kg by mouth daily) alone or AZA (2.2 mg/kg by mouth daily) plus olsalazine (0.5 g by mouth 3 times daily) was best to maintain remission for patients with quiescent corticosteroid-dependent UC over a study duration of 2 years.¹³² There were no significant differences between groups in time to relapse or discontinuation of treatment, Ulcerative Colitis Clinical Activity Index scores, Ulcerative Colitis Disease Activity Index scores, or Inflammatory Bowel Disease Questionnaire scores. However, the number of adverse events and the cost of treatment were significantly higher, and compliance with treatment was poorer with combination therapy (AZA plus olsalazine). The investigators concluded that patients with corticosteroid-dependent UC successfully maintained in remission with AZA are not in need of 5-aminosalicylic acid compounds. The generalizability of these data to patients treated with mesalamine derivatives other than olsalazine has been questioned, however, and further analyses need to be performed to identify if similar trends are seen.

Prevention of postoperative recurrence. It is well recognized that CD almost inevitably recurs after surgical resection.¹⁴⁰ The pattern of recurrence is similar to the preoperative length of the diseased segment and the pattern of inflammatory activity (stricturing or fistulizing). The features of recurrence follow a sequence of endoscopically identifiable lesions at the anastomotic and preanastomotic sites, followed at various intervals (according to the severity of the mucosal lesions) by clinical symptoms. Over the past decade, there has been a series of clinical trials attempting to delay or prevent postoperative recurrence. However, despite these trials, the evidence base remains insufficient to develop a clear consensus on optimal patient selection for postoperative “prophylaxis,” therapeutic agent(s), duration of treatment, or end points for continuing or discontinuing therapy.

Overall, there is an approximate 7%–25% per-year risk of symptomatic recurrence, with a 50% likelihood of recurrent symptoms by 5 years after intestinal resection. The risk of endoscopic recurrence is typically assessed to be higher: 73%–93% by 1 year after resection.^{141,142} Several potential factors have been assessed and suggested as contributing to postoperative recurrence,¹⁴³ including fistulizing versus nonfistulizing disease, number of previous resections, length of resection, site of disease (ileal, ileocolonic, colonic), cigarette smoking, type of surgical anastomosis (end-end, end-side, side-side), and extent of proximal disease.

There have been several controlled studies evaluating the efficacy of various agents in decreasing postoperative recurrence. In a study evaluating the efficacy of metronidazole (20 mg/kg) for 3 months after ileocecal resection versus placebo, there was significant intolerance to medication, limiting the efficacy of medication.¹⁴⁴ The total endoscopic recurrence rates after 3 months were not significantly decreased in the metronidazole group (52% vs 75%). However, severe endoscopic lesions were lower in the active treatment group (13% vs 43%; $P < .02$). Clinical recurrence was only suppressed at 1 year, not at years 2 or 3. Another study that evaluated the efficacy of ornidazole (a metronidazole cogener with presumptive better tolerability) was performed in a prospective randomized fashion at a dosage of 500 mg twice daily for 1 year, initiated within 1 week after ileocecal resection, and found significant reduction of endoscopic relapse rates at 3 months and 1 year.¹⁴⁵ Endoscopic recurrence rates (scored as >1 on a 4-point severity scale) were lower at 3 and 12 months with ornidazole than placebo (34% vs 58.8% [$P = 0.47$] and 53.6% vs 78.8% [$P = .037$], respectively). Clinical recurrence was significantly lower after the first year in the ornidazole-treated patients (8% vs 38%, $P = .0046$); this difference was not apparent at 2 and 3 years, possibly because the drug was discontinued after 1 year. The principal drawback of nitroimidazoles in this setting is the side effects associated with long-term use of these agents. Gastrointestinal intolerance with nausea, a metallic taste, and peripheral neuropathy preclude long-term administration, and the role of these antibiotics is probably as an induction agent to bridge the gap to the effect of immunosuppressives.

In another study, budesonide (6 mg daily) was shown to be ineffective versus placebo for reducing postoperative recurrence of CD.⁶⁴ Endoscopic and clinical recurrence rates were not different between both groups at 3 and 12 months. A subanalysis showed a significant reduction in endoscopic lesions at 12 months with budesonide (32% vs 65% for placebo; $P < .05$) but only in patients operated on for inflammatory luminal disease and not for fibrostenotic disease. There is currently no evidence to support the use of budesonide for postoperative prophylaxis.

The use of 6-MP or AZA has also been assessed in postoperative settings. A larger multicenter trial was initiated evaluating the efficacy of daily doses of 6-MP 50 mg or mesalamine (Pentasa) 3 g versus placebo.¹⁴⁶ End points were endoscopic and clinical recurrence. This double-blind, double-dummy design assessed patients for clinical, radiologic, and endoscopic recurrence following curative Crohn's resection at regular intervals throughout the study period of 24 months. Dropout rates were

considerable in the course of the trial but evenly distributed among the 3 groups. Endoscopic recurrence rates were lower with 6-MP (43%) than placebo (64%; $P = .030$), as were clinical recurrence rates (50% vs 77%; $P = .045$), while radiographic recurrence rates were similar between the groups. There was no apparent benefit of mesalamine versus placebo. Further evaluation of 6-MP at higher doses and perhaps in conjunction with other agents (such as tolerable antibiotics) might represent viable future strategies. Concern over the low dosage of 6-MP used, the rate of patient dropout, the use of an unvalidated clinical assessment score, and the findings of a few patients with clinical recurrences in the absence of endoscopic evidence of disease have led to the call for larger prophylactic trials with higher doses of purine analogues.¹⁴⁷

A separate study compared the use of AZA with mesalamine as postoperative prophylaxis in patients with CD.¹⁴⁸ In this prospective, open-label, randomized study, 142 patients received AZA (2 mg \cdot kg⁻¹ \cdot day⁻¹) or mesalamine (3 g/day) for 24 months; there was no placebo arm. In addition, one half of patients had strictureplasty as part or all of their surgical interventions rather than a curative resection. Clinical relapse was defined as the presence of symptoms with a CDAI score >200 . Surgical relapse was defined as the presence of symptoms refractory to medical treatment or the presence of complications mandating surgical intervention. At 24 months, the risk of clinical relapse was similar in the AZA and mesalamine groups, either when assessed on an intention-to-treat analysis (OR, 2.04; 95% CI, 0.89–4.67) and a per-protocol analysis (OR, 1.79; 95% CI, 0.80–3.97). There was no observable difference with respect to surgical relapse at 24 months between the 2 groups, although post hoc analysis showed AZA to be more effective than mesalamine in preventing clinical relapse in patients with previous intestinal resections (OR, 4.83; 95% CI, 1.47–15.8). A larger proportion of patients receiving AZA withdrew from treatment due to adverse events as compared with those receiving mesalamine (22% vs 8%; $P = .04$). Concerns over the lack of blinding in this study, inclusion of patients without a curative resection of their disease, lower-than-anticipated relapse rates, and lack of statistical power to show a difference between the treatment groups suggest that larger blinded controlled trials are warranted.¹⁴⁹

The findings of these studies, in addition to the expanding use of the purine analogues in IBD due to their proven efficacy in the treatment of active disease and maintenance of remission, have led to the recommendation for use of these agents in patients at high risk for

postoperative recurrences or in whom postoperative recurrence would have substantial deleterious effects.^{147,149}

Recommendations for 6-MP/AZA use.

- When initiating therapy with either 6-MP or AZA, measurement of complete blood count with differential is advocated at least every other week as long as doses of medications are being adjusted. Thereafter, the measurement of complete blood count with differential should be performed as clinically appropriate at least once every 3 months. Periodic measurement of liver-associated chemistries is also advocated. (Grade C)
- Current FDA recommendations suggest that individuals should have TPMT genotype or phenotype assessed before initiation of therapy with AZA or 6-MP in an effort to detect individuals who have low enzyme activity (or who are homozygous deficient in TPMT) in an effort to avoid AZA or 6-MP therapy in these patients and thus avoid potential adverse events. (Grade B)
- Long-term treatment with corticosteroids is undesirable. Patients with chronic active corticosteroid-dependent disease (either CD or UC) should be treated with AZA 2.0–3.0 mg · kg⁻¹ · day⁻¹ or 6-MP 1.0–1.5 mg · kg⁻¹ · day⁻¹ in an effort to lower or preferably eliminate corticosteroid use. Infliximab is another option in this situation, as is combination infliximab/antimetabolite therapy. (Grade A)
- Individual patients with either CD or UC who experience a severe flare of disease requiring corticosteroid treatment or require re-treatment within the year with another course of corticosteroids should be considered for initiation of therapy with AZA 2.0–3.0 mg · kg⁻¹ · day⁻¹ or 6-MP 1.0–1.5 mg · kg⁻¹ · day⁻¹ in an effort to avoid future corticosteroid use. Infliximab is another option in this situation, as is combination infliximab/antimetabolite therapy. (Grade C)
- 6-MP (and likely AZA) is modestly effective for decreasing postoperative recurrence in patients with CD both endoscopically and clinically. Use of this agent should be considered for patients at high risk for postoperative recurrence or in whom postoperative recurrence would have deleterious effects. (Grade B)
- Some studies have shown AZA 2.0–3.0 mg · kg⁻¹ · day⁻¹ or 6-MP 1.0–1.5 mg · kg⁻¹ · day⁻¹ to have

some efficacy in treating and healing perianal and enteric fistulae. (Grade C)

- Thiopurine metabolite monitoring in the treatment of patients with 6-MP or AZA is useful when attempting to determine medical noncompliance and may be helpful for optimizing dose and monitoring for toxicity. (Grade C)
- AZA 2.0–3.0 mg · kg⁻¹ · day⁻¹ or 6-MP 1.0–1.5 mg · kg⁻¹ · day⁻¹ is effective for maintenance of remission in patients with CD regardless of disease distribution. (Grade A)
- AZA 2.0–3.0 mg · kg⁻¹ · day⁻¹ or 6-MP 1.0–1.5 mg · kg⁻¹ · day⁻¹ is effective for maintenance of remission and reducing corticosteroid dose in patients with UC regardless of disease distribution (Grade A). These drugs are also effective in maintaining remission in patients with UC, but data are conflicting and this has not been confirmed by large well-controlled studies.
- Patients with gastrointestinal intolerance (except for fever, pancreatitis, or hypersensitivity reactions) to AZA may be cautiously tried on 6-MP before being considered for other therapy or surgery (Grade C). Similarly, patients with intolerance to 6-MP may be cautiously tried on AZA before being considered for other therapy or surgery. (Grade C)

Methotrexate

Methotrexate has been used in clinical medicine for more than 40 years. This agent was developed initially for the treatment of patients with leukemia. It was synthesized based on knowledge of the 3-dimensional structure of the enzyme dihydrofolate reductase, as identified by x-ray crystallography. This represents one of the earliest examples of a “designer drug.” In the course of the initial experience that demonstrated efficacy in the oncologic area, it was recognized that patients who had leukemia and concomitant psoriasis or rheumatoid arthritis showed improvement in the latter conditions. These observations subsequently led to the use of methotrexate in low doses (5–25 mg) for primary treatment of patients with these conditions and a number of other immune disorders. Over the past decade, evidence has shown that methotrexate has an emerging role for the treatment of patients with CD.

CD. Active symptoms. IM methotrexate (25 mg/wk) has been shown to be beneficial in patients with active CD in a multicenter, double-blind, placebo-controlled 16-week trial.¹⁵⁰ This dosage is effective to induce remission and for corticosteroid sparing in patients

with active CD. In contrast, lower-dosage oral methotrexate has shown less consistent results. A recent study demonstrated efficacy of oral methotrexate (15 mg/wk) trending toward statistical significance,^{151,152} whereas another controlled study showed that methotrexate 12.5 mg orally once a week was not more effective than placebo or low-dosage 6-MP (50 mg/day) in patients with active CD.

Maintenance therapy. A randomized, placebo-controlled trial demonstrated a maintenance benefit of methotrexate 15 mg IM once weekly for patients with quiescent CD.¹⁵³ This 40-week study showed that 65% could maintain remission as long as medication was continued. This group of patients (ie, the 65%) is derived from patients who had been successfully induced into remission with methotrexate 25 mg IM weekly over 16 weeks (thus, this group was preselected for methotrexate responders). The placebo remission rate at 40 weeks was substantially lower and differed statistically from active therapy. Long-term open-label survival analysis has shown parenteral (but not oral) methotrexate to be effective in maintenance of a methotrexate-induced remission in 47% of patients with CD at 48 months.¹⁵⁴

UC. Active symptoms. Despite early optimism from experience in uncontrolled trials, there remains little evidence to support the use of methotrexate in patients with UC. There is continued debate as to whether the controlled trials used optimal dosages of medication and ideal end points. The dosages used to treat patients with CD successfully (25 mg IM weekly) have not been tested in patients with UC in appropriately performed trials. A single small trial (8 patients) has suggested a lack of efficacy of methotrexate (25 mg IM weekly for 16 weeks) in patients with active UC who were refractory to immunomodulators or corticosteroids.¹⁵⁵ A recent retrospective study of oral methotrexate (mean dosage, 19.9 mg/wk) reported a short-term remission rate of 42% that was sustained in 38% of patients for at least 6 months.¹⁵⁶ Further evaluation in appropriately designed and adequately powered studies is needed.

Maintenance therapy. Only 1 randomized, double-blind, placebo-controlled trial of methotrexate in patients with chronic, active UC has been performed thus far. In this study, Oren et al¹⁵¹ compared oral methotrexate (12.5 mg daily) with placebo for 9 months in 67 patients who had received corticosteroids and/or immunosuppressives for at least 4 of the 12 months preceding the study. No statistical significance was noted among the treatment groups in the proportion of patients achieving remission, the time required to achieve remission, or the proportion of patients experiencing a relapse after achieving a remission. Accordingly, the use of

methotrexate cannot currently be recommended for either induction of remission or maintenance therapy in patients with UC outside of controlled trials. An important research priority is to evaluate the efficacy of methotrexate.

Overall, the aforementioned studies suggest that parenterally administered methotrexate is effective for induction of remission, maintenance of medically induced remission, and corticosteroid sparing in patients with chronically active and treatment refractory CD.

Fistulizing CD. Although methotrexate has been shown to be efficacious in the induction of remission in patients with CD, initial controlled trials did not assess the effect of methotrexate on fistula healing. Two retrospective, uncontrolled studies examined the efficacy of parenteral methotrexate in fistulizing CD. Mahadevan et al¹⁵⁷ reported on 16 patients treated with IM methotrexate (25 mg/wk). Fistula closure was successful in 4 of 16 patients, with partial closure in an additional 5 patients, yielding an overall response rate of 56%. Fistula recurrence was noted on reduction of methotrexate dose or with conversion to oral formulation. A second retrospective series by Vandeputte et al¹⁵⁸ examined the effect of parenteral methotrexate on 20 patients with refractory CD, including 8 patients who had a fistula. Although the investigators noted induction of remission in 70% of patients treated with methotrexate, the specific response of patients with fistulizing disease was not reported separately.

Adverse events. Potential toxicities of methotrexate include leukopenia, nausea, vomiting, hepatic fibrosis, and, rarely, hypersensitivity pneumonitis. Hepatic fibrosis is one of the most significant potential sequelae of long-term therapy with methotrexate. A pretreatment liver biopsy is indicated in patients who have abnormal liver-associated laboratory chemistries and in those at potentially increased risk for hepatic toxicity or those who are suspected of having underlying chronic liver disease. Risk factors for hepatotoxicity include obesity, diabetes mellitus, excessive or long-term alcohol intake, elevated baseline transaminase levels, a cumulative dose of methotrexate of >1500 mg total drug dose, and daily dosing of methotrexate.¹⁵⁹ Follow-up liver biopsy, although recommended by some clinicians for patients who have received a cumulative dose in excess of 1.5 g, has not been assessed in controlled clinical trials in IBD. There have been 2 small preliminary, retrospective studies that have suggested that the risk of methotrexate hepatotoxicity in patients with IBD is low.^{160,161} In the absence of adequate biopsy data from patients with CD, the American Rheumatology Association guidelines regarding surveillance for hepatic toxicity are appropriate

to follow.¹⁶² The guidelines recommend liver biopsy during therapy if a majority of aspartate aminotransferase values over 1 year (repeated every 4–8 weeks) are elevated or if the serum albumin value is decreased. Furthermore, reduction in methotrexate dose is recommended in response to an elevated aspartate aminotransferase level. If moderate to severe fibrosis or cirrhosis is found, treatment with methotrexate should be discontinued.

Because weekly dosing with methotrexate is associated with reduced hepatic folate stores,¹⁶³ patients would be theoretically susceptible to a greater potential for liver toxicity at the doses required to achieve the therapeutic benefit. It is also believed that the incidence of liver toxicity and elevation of serum aminotransferase levels are reduced by the routine prophylactic use of folate supplementation; however, this concept has not been formally tested in a controlled fashion in patients with IBD.

Methotrexate is not recognized to adversely affect female fertility.^{164,165} Methotrexate therapy can cause reversible sterility in men, as documented in individual case reports (patients often receiving other chemotherapeutic drugs as well).^{166–168} Methotrexate is embryotoxic, so women of childbearing age using methotrexate must use adequate contraception. Women who wish to become pregnant should discontinue treatment with the drug for at least 3 months before attempting conception. Because folate may be depleted during methotrexate use and folate deficiency is associated with neural tube defects, it is especially important to supplement this vitamin.

Methotrexate is contraindicated in pregnancy (FDA risk category X) because of severe adverse effects on both the fetus and the course of the pregnancy. The most characteristic malformations induced by methotrexate include craniofacial and limb defects and central nervous system abnormalities, including anencephaly, hydrocephaly, and meningomyelocele.^{169,170} Myelosuppression^{171,172} and desquamating fibrosing alveolitis have also been reported in fetuses exposed to methotrexate during pregnancy.¹⁷³

The American Academy of Pediatrics lists methotrexate as contraindicated during breastfeeding because of several potential problems, including immune suppression, neutropenia, adverse effects on growth, and carcinogenesis.¹⁷⁴

Recommendations for methotrexate use.

- Parenteral methotrexate is indicated for induction of remission in patients with active CD. (Grade B)

- Parenteral methotrexate is indicated for maintenance of remission in patients with inactive CD. (Grade B)
- The currently available evidence supports the use of methotrexate for induction of remission with corticosteroid withdrawal in patients with active CD who are corticosteroid dependent. (Grade B)
- Methotrexate maintenance therapy (15–25 mg IM weekly) is effective for patients whose active CD has responded to IM methotrexate. (Grade A)
- Methotrexate IM 25 mg weekly for up to 16 weeks followed by 15 mg IM weekly is effective in patients with chronic active disease. (Grade A)
- Methotrexate is absolutely contraindicated in pregnancy. (Grade B)
- The currently available evidence is insufficient to support the use of methotrexate for the induction or maintenance of remission in patients with active UC. (Grade B)
- Routine monitoring of laboratory parameters, including complete blood counts and liver-associated laboratory chemistries, is recommended in patients who are treated with methotrexate. (Grade C)
- Patients with persistently abnormal liver-associated chemistries should either discontinue therapy with methotrexate or undergo liver biopsy. (Grade C)

MMF

MMF inhibits lymphocyte proliferation by selectively blocking the synthesis of guanosine nucleotide in T cells.¹⁷⁵ Its use in IBD was first proposed as an alternative immunosuppressive in patients intolerant to AZA or 6-MP,¹⁷⁶ and the first controlled trial randomizing 70 patients with chronic active CD to either MMF 15 mg/kg or AZA 2.5 mg/kg suggested equivalent efficacy at 6 months.¹⁷⁷ The implications of this study were confounded by the design, whereby the patients also all received prednisolone 50 mg daily with a weekly taper to 5 mg, with maintenance on 5 mg throughout the 6-month trial. Such was the case as well with a comparative study between the agents in patients with UC, where 24 patients with active disease were randomly assigned to receive MMF 20 mg/kg or AZA (2 mg/kg) in combination with prednisolone 50 mg daily, which was tapered in accord with a standardized protocol.¹⁷⁸ Remission rates were higher in the AZA group compared with the MMF group at 4 weeks (92% vs 67%), 6 months (83% vs 78%), and 1 year (100% vs 88%). The

patients who received AZA did not have any severe adverse events, whereas there were 2 severe adverse events in patients using MMF (bacterial meningitis and recurrent upper airway infection).

Other uncontrolled series have shown variable benefit and high rates of drug intolerance in patients with active CD.^{179–183} At present, there are inadequate data to suggest that individuals with IBD should be treated with MMF, and the safety concerns, including reports of inducing a colitis with histologic changes similar to those seen in graft-versus-host disease or CD, make it difficult to justify its use.^{184,185}

Cyclosporine

IV cyclosporine. Cyclosporine was first discovered by Borel et al in the 1970s and soon revolutionized the field of organ transplantation.¹⁸⁶ Both cyclosporin A and FK506 (tacrolimus) competitively bind to and inhibit calmodulin-dependent calcineurin, leading to suppression of T-cell and immunoglobulin E receptor signaling pathways,¹⁸⁷ although each drug binds to a different intracellular immunophilin receptor.¹⁸⁸ Use of cyclosporine has expanded beyond the transplant world to a myriad of immune-mediated diseases, including IBD.

The emergence of cyclosporine as an effective therapy for the treatment of severe, IV corticosteroid-refractory UC was first suggested by successful open-label trials in the 1980s and early 1990s.^{189–192} These led to the landmark 1994 randomized placebo-controlled trial in which the addition of IV cyclosporine (4 mg/kg daily) to the treatment of patients with severe colitis despite at least 7 days of IV corticosteroids resulted in a response (defined as a score <10 on a modified Truelove and Witts' scale on days 7 and 8, with a decrease of ≥ 3 points and the possibility to discharge the patient) in 9 of 11 patients (82%) within a mean of 7.1 days as compared with none of the 9 patients receiving placebo.¹⁹³ Subsequent retrospective studies have also confirmed response rates of 76%–86%.^{134,194,195} Those patients who responded to IV cyclosporine were subsequently treated with oral cyclosporine 8 mg \cdot kg⁻¹ \cdot day⁻¹ for 6 months; 4 of the 9 underwent colectomy.¹⁹⁶

The inability of cyclosporine alone to maintain these clinical responses or remissions¹⁹⁷ led to the coadministration of the purine analogues 6-MP or AZA as long-term maintenance therapies,^{135,198} with up to 80% of initial cyclosporine successes avoiding colectomy with the use of one of these maintenance agents.¹³⁴ These studies suggest a protocol of “bridging” the severely ill patient with UC to a remission induced with IV cyclosporine and subsequently initially maintained with a combination “triple therapy” (oral prednisone, oral cy-

closporine, and oral 6-MP or AZA), with subsequent tapering of the corticosteroid and cyclosporine in the ensuing months and long-term maintenance solely using the purine analogue.^{199,200} Although there has been variation between studies, many studies used the following protocol.

- Initiated the purine analogue before or at the time of discharge. The dose varies between studies; some used a low dose (ie, 50–75 mg daily of either 6-MP or AZA with an increase to the desired target dose), whereas others dosed 6-MP at 1.0–1.5 mg/kg and AZA at 1.5–2.5 mg/kg, with dose adjustments as necessary due to safety- or efficacy-related issues.
- Converted the patient from IV to oral cyclosporine before or at discharge. The initial conversion from IV to oral dosing is a doubling of the total daily dose, split into a twice-daily dosing regimen. For example, a patient with desired blood cyclosporine levels while receiving a continuous IV infusion of 200 mg daily would be switched to oral cyclosporine (Neoral; Novartis Pharmaceuticals Corp, East Hanover, NJ) 200 mg by mouth twice daily. The oral dose would subsequently be titrated to achieve a trough blood level greater than 200 ng/mL.
- Weaning off of oral cyclosporine over the next few months.
- Continuation of corticosteroids on discharge (if received while on IV cyclosporine), with subsequent tapering off over the next few months.
- Patients treated with triple therapy also need to receive prophylaxis against *Pneumocystis carinii*, because deaths due to pneumonia from this organism have been reported in patients with colitis receiving this combination of immunosuppressants.^{194,201}

There are a variety of assays for cyclosporine, and they do not necessarily correlate to each other or to the patients' clinical state. While earlier studies used high-performance liquid chromatography and polyclonal radioimmunoassay, subsequent studies have relied on monoclonal radioimmunoassay or other immunoassays.^{202,203} Many of the IBD studies specify high-performance liquid chromatography or monoclonal radioimmunoassay target levels of 350–500 ng/mL for IV cyclosporine and 200–350 ng/mL for oral therapy.

Cyclosporine monotherapy has also been studied in patients with severe UC^{189,204} and shown to be as effective as monotherapy with methylprednisolone. In a single-center, double-blinded, randomized trial, 9 of 14 patients (64%) receiving IV cyclosporine 4

$\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ had a response (on the Lichtiger-modified¹⁹³ Truelove and Witts' scale) compared with 8 of 15 patients (53%) who received methylprednisolone 40 mg daily ($P = .4$).²⁰⁵ AZA was started or continued in all of the patients who initially responded to cyclosporine but only in 3 of the 8 methylprednisolone responders, as reflected in 12-month remission rates of 78% versus 37%, respectively. The lack of serious infections in this study, where the patients did not receive prophylaxis against *P carinii*, was touted by the investigators as proof that monotherapy is safer than combination therapy. Comparative IV studies of cyclosporine monotherapy versus dual therapy with cyclosporine and corticosteroids have not been conducted, leaving this safety claim unsubstantiated, and the failure of monotherapy to achieve response rates anywhere near the 80% range suggests that this is more appropriate for patients with a contraindication to receiving corticosteroids.²⁰⁶

Lower doses of IV cyclosporine have also been shown to be effective in patients with severe UC. In a single-center double-blinded trial, 73 patients were randomized to continuous infusion with IV cyclosporine dosed at 2 or 4 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for 8 days.²⁰⁷ Unlike the previous studies, these patients did not necessarily fail to respond to IV corticosteroid therapy; in fact, only 55%–60% of patients entered the study failing to respond to either oral or IV corticosteroids. Doses were adjusted to achieve blood levels between 150 and 250 ng/mL in the low-dose group and between 250 and 350 ng/mL in the high-dose group. The primary end point was a score of <10 (and decrease of ≥ 3 points) on the Lichtiger-modified Truelove and Witts' scale.¹⁹³ This was reached by 85% in the low-dose group and 84% in the high-dose group, with a median time to response of 4 days in both groups. There were similar colectomy rates, changes in C-reactive protein levels, sigmoidoscopy scores, and adverse event rates between the 2 groups. To maintain the prespecified range of serum cyclosporine levels, dose adjustments resulted in mean cyclosporine doses of 1.82 mg/kg in the low-dose group and 2.65 mg/kg in the high-dose group ($P < .0001$), achieving mean blood levels of 237 and 332 ng/mL, respectively ($P < .0001$). It is not known whether low-dose cyclosporine will perform as well in the sicker group of patients failing to respond to therapy with IV corticosteroids.

The success of IV cyclosporine in the treatment of patients with luminal CD has been less impressive. Open-label experiences have had mixed results for the induction of response and poor maintenance data.^{194,208–212} Given these disappointing results and concerns over short-term and long-term toxicities with this agent, cyclosporine is typ-

ically not recommended for use in patients with luminal CD.

There have been no published, randomized, placebo-controlled trials specifically designed to evaluate the efficacy of IV cyclosporine on fistula closure in patients with CD. In an open-label study, Present and Lichtiger evaluated 16 patients with fistulizing CD and treated them with IV cyclosporine (4 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) as a continuous infusion.²¹³ Overall, 88% (14 patients) responded acutely and complete closure of the fistulas was observed in half of these patients. There were 9 of 10 patients with fistulas refractory to AZA or 6-MP that responded to cyclosporine. These results were then supplemented by a comprehensive review of the literature including 39 patients with fistulizing CD who had been treated with cyclosporine.²¹² Among the patients in this group, 90% of the patients responded; however, relapse in the absence of oral cyclosporine was quite high (82%). Fistulas successfully closed with IV cyclosporine (5 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for 2 weeks) were successfully maintained using a combination of oral cyclosporine (for 10 weeks), prednisolone (tapered over 3 months), and AZA.²¹⁴ These results indicate that successful healing of Crohn's fistulas with IV cyclosporine may be best maintained with short-term treatment with oral cyclosporine and corticosteroids, together with long-term treatment with AZA or 6-MP.²¹⁵

Oral cyclosporine. The use of oral cyclosporine has been plagued by multiple factors limiting the absorption in patients with IBD.²⁰² In an effort to improve the bioavailability of orally administered cyclosporine (bioavailability of 12%–35%), microemulsion formulations of cyclosporine (Neoral, Gengraf [Abbott Laboratories, North Chicago, IL] were developed.²¹⁶ The bioavailability of the microemulsion formulations relative to the standard oral formulation is markedly increased (145%–239%).^{216,217} Similar to standard oral cyclosporine, the bioavailability of the oral microemulsion formulation of cyclosporine is the same as a gelatin capsule of microemulsion of cyclosporine.²¹⁸ Also, the microemulsion formulation is therapeutically similar to the standard oral cyclosporine formulation in transplant recipients.²¹⁹

There have been no prospective controlled trials of oral cyclosporine in the treatment of patients with UC. Uncontrolled trials have often shown success at induction of response or remission, while maintenance data have been less convincing. One review of 20 studies in 185 patients calculated an overall response (avoidance of colectomy) in 68%, with only 42% maintaining response after discontinuation of therapy.²⁰² Studies using the Neoral microemulsion cyclosporine formulation suggest that micro-

emulsion cyclosporine may be as effective as standard IV or oral cyclosporine in severe UC with less potential toxicity.^{220–222} In the future, prospective randomized controlled trials will be needed to assess the safety and efficacy of microemulsion cyclosporine compared with standard oral and IV cyclosporine.

The use of oral cyclosporine in patients with CD has been studied in 4 large, multicenter controlled trials; only high-dose therapy seems to be effective. Success rates were higher with active therapy (59% vs 32%; $P = .03$) among 71 patients with active CD randomized to either oral cyclosporine (median dosage of $7.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) or placebo for 3 months.²²³ Although the cyclosporine worked quickly (within 2 weeks) and continued to show efficacy during a 3-month taper,²²³ stopping therapy resulted in disease relapse.²²⁴ Unfortunately, the 3 other studies showed no benefit of oral cyclosporine $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ as compared with placebo.^{225–227} In fact, in the maintenance study arms, there was a trend toward harm²²⁸ in the patients receiving cyclosporine in both the Canadian²²⁶ and European trials.²²⁵ A recent Cochrane analysis concluded that the use of oral cyclosporine in patients with CD is not justified, and the use of higher doses or IV cyclosporine is also not supported by the existing literature and is unwarranted given the potential side effects.²²⁹

Cyclosporine enemas. Enema formations of cyclosporine with varying doses have been studied in uncontrolled trials on a handful of patients.^{230–233} An initial review found response rates varying from 50% to 75%, with sustained response rates after discontinuation of therapy at only 36%.²⁰² A subsequent placebo-controlled trial in 40 patients with left-sided UC found no benefits with nightly 350-mg cyclosporine enemas over placebo (response rates of 45% vs 40%, respectively).²³⁴

Adverse events. The most common side effects due to cyclosporine therapy in patients with IBD include hypertension, seizures, paresthesias, tremor, gingival hyperplasia, hypertrichosis, electrolyte abnormalities, opportunistic infections, and nephrotoxicity.⁹⁵ Prophylaxis against *P carinii* is recommended, especially if used in conjunction with other immunosuppressants. Complete blood counts, serum chemistries, and cyclosporine blood levels should be followed up regularly while on therapy, and careful monitoring for side effects is critical.⁹⁵ Dose reduction is advised in patients with low serum cholesterol levels or who develop side effects.¹⁹⁹

Recommendations for cyclosporine use.

- IV cyclosporin A is effective as a means of avoiding surgery in patients with severe corticosteroid-refractory UC. (Grade A)
- IV cyclosporine at $2\text{--}4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ or colectomy should be considered if a patient with severe UC has failed to respond to medical therapy with 7–10 days of high-dose oral or parenteral corticosteroid therapy. (Grade B)
- Concomitant administration of IV corticosteroids is recommended, but not required, to induce a clinical response in patients with severe UC receiving IV cyclosporine. (Grade B)
- A response or remission induced with IV cyclosporine in patients with IBD typically requires continuation of therapy with oral cyclosporine for a few months, along with a tapering dose of corticosteroids, initiation of AZA or 6-MP therapy, and prophylaxis against *P carinii* (Grade B). AZA or 6-MP should be continued as maintenance therapy. (Grade B)
- Oral cyclosporine is efficacious in patients with corticosteroid-refractory UC (Grade C) but requires AZA or 6-MP for maintenance of remission. (Grade C)
- Neither IV (Grade C) nor oral (Grade A) low-dose cyclosporine has proven efficacy in patients with luminal CD. High-dose oral cyclosporine (7.6 mg/kg) has short-term efficacy in patients with CD. (Grade B)
- IV cyclosporine is effective for the treatment of patients with fistulizing CD (Grade B). AZA or 6-MP should be used for maintenance of fistula closure. (Grade C)

Other Calcineurin Inhibitors

Tacrolimus (FK506) is a fungus (*Streptomyces*)-derived immunosuppressant that has a mechanism of action similar to that of cyclosporine.²³⁵ The relatively low bioavailability (ranging from 21% to 27%) is likely due to its poor aqueous solubility. Tacrolimus does not depend on bile or mucosal integrity for absorption, resulting in less interpatient variability than with standard oral cyclosporine. These features suggest potential distinct advantages over cyclosporine, especially for patients with small bowel CD.

In an open-label, multicenter trial of tacrolimus in children with severe UC or Crohn's colitis, 69% (9/13) responded to 2- to 3-month therapy with tacrolimus 0.1

mg/kg given as a divided dose twice daily (adjusted for blood levels between 10 and 15 ng/mL). 6-MP or AZA was added as a corticosteroid-sparing agent 4–6 weeks after treatment with tacrolimus was instituted, but at 12 months only 38% of patients had avoided colectomy.²³⁶ In another study, 38 patients with refractory UC (n = 33) or indeterminate colitis (n = 5) received tacrolimus as either an IV infusion (0.01–0.02 mg/kg) followed by 0.1–0.2 mg/kg orally or as the oral dose only.²³⁷ Patients who responded (47%) received AZA or 6-MP, and corticosteroids were tapered, followed by a reduction in the dose of tacrolimus for a mean of 7.6 months. The overall colectomy rate was 34%, but one half of the patients with a minimum follow-up of 2 years required a colectomy. Adverse event rates were similar in both groups, including tremor, hyperglycemia, hypertension, and infections.

In a smaller study, therapy with oral tacrolimus (0.15 mg/kg) was effective in two thirds of 11 patients with severe UC, with 67% keeping their colons at a median follow-up of 21 months, using AZA as maintenance therapy.²³⁸ Two patients had severe hematologic side effects.

The use of tacrolimus in Crohn's fistulas has been the subject of a few small uncontrolled experiences, with variable results.^{239,240} In a randomized, double-blind, placebo-controlled, multicenter clinical trial, 48 patients with draining perianal or enterocutaneous fistulas were randomized to oral tacrolimus 0.2 mg · kg⁻¹ · day⁻¹ or placebo for 10 weeks.²⁴¹ The primary outcome measure of fistula improvement (defined by closure of at least 50% of draining fistulas and maintenance of that closure for at least 4 weeks) was achieved by 43% versus 8% of patients receiving placebo (*P* = .004). However, closure rates of all fistulas for at least 4 weeks were not different between the groups. Improvement in Crohn's fistulas refractory to other conventional therapy, including infliximab, was recently reported in 5 of 10 patients receiving oral tacrolimus (0.05 mg/kg every 12 hours). Unlike the other studies of tacrolimus and cyclosporine in fistulous CD, concomitant immunosuppressive therapy was tapered, and the patients were maintained solely on tacrolimus with no reported major toxicities, likely due to the low dose studied.

Adverse events reported in the various studies included headache, increased serum creatinine level, nausea, insomnia, leg cramps, paresthesias, and tremors. Typically, these resolved with dose reduction. Lower doses of tacrolimus have yet to be adequately studied for efficacy and safety in patients with IBD.

Infliximab

Tumor necrosis factor (TNF)- α is a proinflammatory cytokine with a central role in the pathogenesis of CD.²⁴² Infliximab is a chimeric monoclonal antibody directed against TNF- α that was introduced into clinical practice in the United States in October 1998.

Infliximab is approved by the FDA for reducing the signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active CD who have had an inadequate response to conventional therapy.²⁴³ Conventional therapy was not defined in the FDA approval and could include mesalamine, corticosteroids, antibiotics, or immunomodulators such as AZA, 6-MP, or methotrexate. In addition, infliximab is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing CD. Recently, infliximab also received approval from the FDA for the treatment of patients with UC. Infliximab is indicated for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy.²⁴⁴ The recommended dose of infliximab is 5 mg/kg given as an induction regimen at 0, 2, and 6 weeks, followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. In CD, patients who respond and then lose their response may be considered for treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing, and consideration should be given to discontinuing treatment with infliximab in these patients.²⁴⁴

Induction of remission in active CD. In the first published study of the clinical use of this agent in CD, van Dulleman et al showed that infliximab produced a rapid, dramatic clinical and endoscopic improvement in 8 of 10 patients treated.²⁴⁵ In the first placebo-controlled, randomized study, 108 patients received a single dose of infliximab (5, 10, or 20 mg/kg body wt) or placebo.²⁴⁶ A clinical response was defined as a decrease in CDAI score of more than 70 points after 4 weeks. In patients who received the 5-mg/kg dose, 81% (22 of 27 patients) responded compared with a 50% response (14 of 28) in the 10-mg/kg group, a 64% response (18 of 28) in the 20-mg/kg group, and a 17% response (4 of 24) in the placebo group. The differences in the responses of the combined infliximab groups compared with placebo were significant (*P* < .001). Clinical remission (CDAI score <150) was achieved in 33% of patients treated with infliximab compared with 4% of patients in the placebo

group ($P = .005$). Clinical improvement was maintained for 12 weeks in 41% of patients. Concomitant medication use (immunosuppressive agents, aminosalicylates, or corticosteroids) and disease localization did not have any influence on response to therapy, and the dose of 5 mg/kg body wt was the most effective.²⁴⁶

Maintenance of remission in CD. The efficacy and safety of infliximab for maintaining remission in patients with CD was first assessed in a randomized, double-blind, multicenter, placebo-controlled, parallel-group trial.²⁴⁷ The study was performed in patients who had a clinical response to infliximab at 4 weeks in the prior study reported by Targan et al.²⁴⁶ The study enrolled 73 patients and treated them with 4 repeated infusions of either infliximab ($n = 37$) or placebo ($n = 36$) every 8 weeks (weeks 12, 20, 28, and 36). The dose of infliximab used was 10 mg/kg body wt. The last assessment at 44 weeks occurred 8 weeks after the last infusion of either drug or placebo. Corticosteroid tapering was allowed at the discretion of the investigator, and no increase in corticosteroid dose was permitted. The primary end points were clinical response (defined as a ≥ 70 -point decrease in CDAI score) and remission (defined as a CDAI score < 150) at each 4-week interval and the proportion of patients who discontinued due to lack of efficacy. At 44 weeks (8 weeks after the last infusion), 52.9% of patients were in remission on maintenance infliximab therapy compared with 20% on placebo maintenance therapy ($P = .013$).

In a subsequent larger maintenance trial, ACCENT I, a total of 580 patients with active CD (CDAI score ≥ 220) were enrolled at 55 sites. Eligible patients had CD for at least 3 months with a CDAI score between 220 and 400. Patients remained on a stable dose of anti-inflammatory or immunosuppressive therapy if they were taking these medications, while corticosteroid tapering was allowed. Patients previously treated with infliximab were excluded. Responders to a single infusion of infliximab 5 mg/kg (assessed at week 2) were randomized to maintenance therapy with infliximab or placebo at weeks 2 and 6 and then every 8 weeks thereafter until week 46.²⁴⁸ Infliximab was given either as 5 mg/kg with each dose or as 5 mg/kg at weeks 2 and 6 and then 10 mg/kg every 8 weeks thereafter. In the primary analysis of this study, there were coprimary end points of clinical remission at week 30 and clinical response at week 54. Infliximab was superior to placebo for achieving remission at 30 weeks for both the lower-dose regimen ($P = .003$) and the higher-dose regimen ($P = .002$). Patients who received infliximab had a significantly longer time to loss of response than patients who received placebo ($P = .0002$ comparing the combined infliximab groups vs

placebo). At week 54, about 3 times as many patients (29% vs 9%) on infliximab versus placebo had discontinued treatment with corticosteroids while maintaining clinical remission. This study showed that the 3-dose induction regimen at weeks 0, 2, and 6 is more effective at inducing remission than single-dose induction therapy and that the benefits of infliximab in CD could be maintained over the longterm in patients treated with systematic maintenance therapy.

Episodic versus maintenance treatment. Rutgeerts et al performed a post hoc analysis on all patients who entered the ACCENT I study, including not only those patients who responded to an initial single dose of infliximab but also the nonresponders.²⁴⁹ The efficacy of regularly scheduled re-treatment versus episodic re-treatment with infliximab for patients with CD was compared. The study included 573 patients with CD with a CDAI score between 220 and 400. All patients received infliximab 5 mg/kg at week 0 and then were randomized into 3 groups: (1) 188 received placebo at 2 and 6 weeks and every 8 weeks to week 46, (2) 192 patients received infliximab 5 mg/kg at weeks 2 and 6 and every 8 weeks thereafter to week 46, and (3) 193 received infliximab 5 mg/kg at weeks 2 and 6 and then infliximab 10 mg/kg every 8 weeks to week 46. For all 3 groups, after week 14, patients could cross over to treatment with infliximab at a dose 5 mg/kg higher than their assigned dose if there was a loss of response with the scheduled therapy. In this manner, the placebo group could be considered an episodic treatment group and compared with systematic maintenance therapy with infliximab 5 mg/kg and 10 mg/kg every 8 weeks. The results showed that regularly scheduled treatment with infliximab 5 mg/kg and 10 mg/kg achieved a statistically significant ($P < .05$) higher proportion of patients in remission at weeks 10, 14, 22, and 46 compared with the episodic treatment group. Also, 44% of patients in the regularly scheduled treatment groups had mucosal healing at week 54 compared with 18% in the episodic treatment group ($P = .014$). Antibodies to infliximab were found in a lower proportion of patients treated on a regular schedule than episodic treatment (9% with the 5-mg/kg dose, 6% with the 10-mg/kg dose, and 28% with episodic treatment).²⁴⁹ Patients who received infliximab on a regular schedule had fewer CD-related hospitalizations ($P = .014$) and fewer surgeries for CD ($P = .01$) than those on episodic treatment.²⁴⁹ Serious infections occurred in 3%–4% in all 3 groups, and the rates of toxicity were also similar among the 3 groups. Only a minority of patients in any of the 3 groups remained in remission for 1 year when treated with the initial assigned dose of infliximab.^{249,250} However, two thirds of the patients in

all 3 groups maintained remission if the dose of infliximab was increased during the year of treatment.^{249,250} To date, no studies have shown if starting AZA, 6-MP, or methotrexate at the time infliximab is started improves the maintenance effect of infliximab.

Infliximab therapy can cause the formation of antibodies to infliximab (ATI). The development of ATI correlates with an increased risk of infusion reactions and, during episodic therapy, with a shorter duration of response because infliximab concentrations are lower.²⁵¹ In a cohort of 125 consecutive patients with CD treated episodically with infliximab, ATI were detected in 61%.²⁵¹ The presence of higher concentrations of ATI (>8 $\mu\text{g/mL}$) predicted a shorter duration of response (35 vs 71 days) and a 2.4-fold higher relative risk of infusion reactions than in patients with a lower concentration of absence of ATI.²⁵¹ The test results of measurement of ATI in serum samples obtained between infliximab infusions are often indeterminate. Inconclusive test results for ATI have been defined as absence of circulating ATI with detectable concentrations of infliximab in the serum sample.²⁵² In the ACCENT I study, inconclusive test results for ATI were found in 10% of patients who received episodic treatment with infliximab and in 33% and 36%, respectively, of patients receiving regularly scheduled dosing with infliximab 5 mg/kg and 10 mg/kg.²⁵² Longer follow-up of patients with indeterminate ATI results has now shown that the vast majority of these patients are in fact negative for ATI.²⁵² In ACCENT I, ATI were detected in significantly more patients treated with infliximab episodically than those treated with regularly scheduled maintenance dosing at 5 mg/kg or 10 mg/kg (30% vs 10% and 7%, respectively).²⁵² In the ACCENT I trial, where the majority of patients received regularly scheduled maintenance therapy, there was no significant difference in the clinical remission rate (41% vs 39%) or in the clinical response rate for antibody-positive patients compared with antibody-negative patients. In contrast, Farrell et al showed that during episodic therapy, loss of the initial response and infusion reactions after infliximab therapy were strongly related to ATI formation and antibody level.²⁵³ Among 53 patients with CD who received 1–3 infliximab infusions, 11 of 17 (73%) who lost their initial response were ATI positive compared with 0 of 21 who were continuous responders after a median follow-up of 20 weeks.²⁵³ In a placebo-controlled trial, pretreatment with hydrocortisone 200 mg IV was associated with ATI in 26% compared with ATI in 42% ($P = .06$) of patients receiving placebo, and antibody levels were lower in the pretreated group (1.6 vs 3.4 $\mu\text{g/mL}$; $P = .02$) as well.¹⁷⁴ However, administration of another infliximab infusion within 8 weeks of

the prior dose was the factor most strongly associated with a decreased risk of ATI development in this study.²⁵³

The common theme in these studies is that regularly scheduled maintenance therapy with infliximab is substantially less immunogenic than episodic treatment. ATI develop less frequently with maintenance therapy and have less impact on outcomes even when they do. For this reason, along with the better efficacy results seen with maintenance therapy in the ACCENT I study, regularly scheduled maintenance therapy with infliximab every 8 weeks is the preferred treatment strategy.

An additional strategy for the prevention of ATI is the use of a concomitant immunomodulator. The role of concomitant immunotherapy with 6-MP, AZA, or methotrexate along with infliximab in the treatment of patients with CD is not well defined. In the ACCENT I study, 50% of the patients who received a concomitant baseline immunosuppressive maintained clinical response at week 54 compared with 41% of those not receiving such treatment, but this difference was not significant.¹⁶⁹ Although 3 previously described studies have shown that concomitant immunotherapy reduces the risk of ATI^{248,251,253} and 2 of the studies showed that the presence of high-titer ATI reduces the response to infliximab,^{251,253} there is thus far no prospective study to compare the response and remission rates with infliximab in patients with and without concomitant immunosuppressive treatment. Although it is clear that in the treatment of patients with CD a single dose of infliximab without concomitant immunotherapy is immunogenic and is associated with a shortened duration of benefit, it is unclear if concomitant immunosuppressive therapy adds long-term benefit to regularly scheduled dosing of infliximab.²⁵⁴ Likewise, it is unclear if infliximab can have a bridging effect to transition patients from corticosteroids to AZA or 6-MP, with the infliximab discontinued thereafter. Lemann et al showed in a placebo-controlled trial that infliximab could bridge from corticosteroid dependency to AZA or 6-MP for up to 6 months, with remission rates off corticosteroids of 83% with infliximab given in 3 doses over 6 weeks and 41% with placebo ($P < .009$), but no significant difference was seen after 24 weeks.²⁵⁵ It is well established that methotrexate plus infliximab is superior to either drug alone in the treatment of patients with rheumatoid arthritis,²⁵⁶ but the benefit of combining methotrexate with infliximab for patients with CD is unproved. The downside of using concomitant immune suppression is the greater risk of serious and opportunistic infection,²⁵⁴ and the risk/benefit ratio of using concomitant immuno-

suppressives is unknown. These are important questions that must be addressed in future studies.

Fistulizing CD. There have been 2 randomized, double-blind, controlled studies that evaluated the efficacy of infliximab for treatment of patients with fistulizing CD.^{257,258} Present et al treated 94 patients with cutaneous fistulas, including 85 with perianal fistulas, with infliximab at weeks 0, 2, and 6 (5 mg/kg or 10 mg/kg) or placebo. Complete closure for 1 month was reported in 13% of patients receiving placebo but in 55% ($P = .002$ compared with placebo) of patients receiving infliximab 5 mg/kg and in 38% ($P = .02$ compared with placebo) of patients receiving infliximab 10 mg/kg.²⁵⁷ The median duration of remission was 3 months. In the second study (ACCENT II), maintenance therapy with infliximab in patients with fistulizing CD was studied.²⁵⁸ A total of 306 patients were initially treated with infliximab 5 mg/kg at weeks 0, 2, and 6, and responders subsequently were randomized to placebo or infliximab 5 mg/kg at 8-week intervals from week 14 until the end of the study at week 54. At week 14, 195 of 306 patients (69%) showed a response to the infliximab induction therapy with closure of at least 50% of the fistulas. The primary end point of this study was "time to loss of response to therapy." The median time to loss of response was 14 weeks in the placebo group and >40 weeks on infliximab ($P < .001$). At week 54, 39% of patients receiving maintenance infliximab 5 mg/kg every 8 weeks and 19% of patients receiving placebo demonstrated complete closure of all fistulas ($P = .009$). Among the patients who had no response at the time of randomization to maintenance therapy, 16% of those patients who subsequently received placebo responded compared with a response in 21% of those patients who subsequently received infliximab ($P = .6$), suggesting that patients with fistulizing CD who have not demonstrated a response after a 3-dose induction regimen do not benefit from continued maintenance therapy. Thus, maintenance therapy should only be given to patients who respond to induction therapy. Among patients who initially responded to infliximab 5 mg/kg but subsequently lost the response, 57% responded to a higher dose of infliximab of 10 mg/kg.²⁵⁸ Based on the currently available data, it appears that continuous maintenance therapy with infliximab dosing every 8 weeks is necessary to maintain symptomatic remission of fistulas. Even so, magnetic resonance imaging scanning has shown that asymptomatic cutaneous fistula tracks are often not completely obliterated.^{259–261} In a post hoc analysis of the data from the ACCENT II study, 25 of 138 women (18.1%) had draining rectovaginal fistulas. The overall response rate at week 14 for closure of the fistulas was

64%, which was similar to the response rate for patients with other types of fistulas.²⁶² Infliximab is FDA approved for the treatment of patients with rectovaginal fistulas. Currently, there are little data on the use of infliximab for internal fistulas (eg, enterovesical fistulas).²⁶³

UC. Five controlled trials studying infliximab for the treatment of patients with UC have been reported.^{264–268} In a small study by Sands et al, 4 of 8 patients with corticosteroid-refractory UC were considered treatment successes 2 weeks after a single infusion of infliximab compared with 1 of 3 patients receiving placebo.²⁶⁴ In contrast, a study by Probert et al found no statistical difference in remission rates at 6 weeks (39% vs 30%) between infliximab-treated patients and placebo-treated patients with corticosteroid-resistant UC.²⁶⁸ Both of these studies were probably statistically underpowered. The results of 2 larger randomized placebo-controlled trials, ACT 1 and ACT 2, were recently reported.²⁶⁹ In each of these 2 studies, 364 patients who were unresponsive to at least 1 standard therapy, including oral 5-aminosalicylates (ACT 2 only), corticosteroids, or immunosuppressants, were randomized to receive infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo.^{265,266} Patients in ACT 1 were treated at weeks 0, 2, and 6 and then every 8 weeks through week 46, with evaluation at week 54.²⁶⁵ Patients in ACT 2 were treated at weeks 0, 2, and 6 and then every 8 weeks through week 22, with the last evaluation at week 30.²⁶⁶ In both studies, patients continued their immunomodulators and aminosalicylates throughout the trial, while corticosteroid tapering was allowed after week 8. In ACT 1, the clinical response rates at weeks 8, 30, and 54 were significantly higher for the groups treated with infliximab 5 mg/kg (69%, 52%, and 46%, respectively; $P < .001$ for infliximab vs placebo at all points) or 10 mg/kg (62% [$P < .001$ vs placebo], 51% [$P = .002$ vs placebo], and 44% [$P < .001$ vs placebo, respectively]) than for the placebo group (37%, 30%, and 20%, respectively). Similarly, remission rates at weeks 8, 30, and 54 were significantly higher for the groups treated with infliximab 5 mg/kg (39%, 34%, and 35%, respectively) and infliximab 10 mg/kg (32%, 37%, and 34%, respectively) than for the placebo group (15%, 16%, and 17%, respectively).^{265,269} The P values comparing infliximab with placebo for the remission end point were all very highly statistically significant ($P < .001$ for all except the 30-week result for 5 mg/kg; $P = .002$). Mucosal healing was seen after 8 weeks in 62% of patients receiving infliximab 5 mg/kg, 59% of patients receiving infliximab 10 mg/kg, and 34% of patients receiving placebo ($P < .001$ for both infliximab groups compared with placebo). The mucosal

healing benefit was maintained at week 30 (infliximab 5 mg/kg, 50%; infliximab 10 mg/kg, 49%; placebo, 19% [$P < .001$]) and at week 54 (infliximab 5 mg/kg, 46%; infliximab 10 mg/kg, 47%; placebo, 18% [$P < .001$]).²⁶⁹ In the ACT 2 study, which was a 30-week trial, the clinical response rates at weeks 8 and 30 were significantly higher for the groups treated with infliximab 5 mg/kg (65% and 47%, respectively) or 10 mg/kg (69% and 60%, respectively) than for the placebo group (29% and 26%, respectively). In each case, these results were highly statistically significant ($P < .001$). The clinical remission rate in ACT 2 at week 8 was 34% in the group receiving infliximab 5 mg/kg, 28% in the group receiving infliximab 10 mg/kg, and 6% in the placebo group ($P < .001$ for both comparisons).²⁶⁶ At week 30, the remission rates were 26% in the group receiving infliximab 5 mg/kg, 36% in the group receiving infliximab 10 mg/kg, and 11% in the placebo group ($P < .001$ for each infliximab group vs placebo). Mucosal healing at week 8 was achieved in 60% and 62% of the 2 infliximab groups compared with 31% of the placebo group ($P < .001$ for each infliximab group vs placebo). At week 30, mucosal healing was observed in 46% and 57% of the infliximab-treated patients compared with 30% of the placebo group ($P = .009$ and $P < .001$, respectively). Taken together, the results of the ACT trials clearly establish the efficacy of infliximab in the treatment of active UC that has insufficiently responded to conventional therapies.²⁶⁹ It should be noted that all subjects in ACT 1 and ACT 2 were outpatients; these studies did not examine the efficacy of infliximab in the treatment of hospitalized patients with UC failing to respond to IV corticosteroids. In a separate recent study, 45 patients with moderate-severe to severe UC refractory to IV corticosteroids were treated with a single dose of infliximab 5 mg/kg versus placebo. Seven of 24 patients in the infliximab group and 14 of 21 patients in the placebo group ($P = .017$) required colectomy by 3 months.²⁶⁷

Extraintestinal manifestations. Extraintestinal manifestations occur in more than 20% of all patients with CD (involving the skin, joints, eyes, and so on) and often represent a major therapeutic challenge, frequently requiring an aggressive therapy approach, such as the use of cyclosporin A in case of pyoderma gangrenosum. In a prospective open study of patients with CD, 27 of 59 evaluable patients (46%) were asymptomatic for arthritis at week 12 after 3 doses of infliximab.²⁷⁰ There are numerous case reports of favorable results using infliximab to treat pyoderma gangrenosum.²⁷¹ There are case reports of the benefit of using infliximab in the treatment of cutaneous vasculitis and ulcerations of the oral cavity.²⁷¹

Side effects. Infections. As with other immunosuppressive drugs, patients treated with infliximab can be expected to develop more infections than otherwise healthy individuals not receiving immunosuppressive therapy. The occurrence of infections in infliximab clinical trials has not been statistically higher in the infliximab-treated groups than in the placebo groups, perhaps because some patients in both the infliximab and placebo arms were also receiving other immunosuppressive therapies. Nonetheless, in postmarketing experience, bacterial infections in all organs have been described, as well as mycoses (histoplasmosis, coccidioidomycosis, nocardiosis, and candidiasis). Listeriosis has also been observed in individuals treated with infliximab²⁷²; thus, it seems logical that nonpasteurized dairy products and soft cheese should be avoided. Colombel et al reported the clinical experience of the Mayo Clinic with more than 500 patients treated with infliximab.²⁷³ Twenty of 500 patients experienced a serious infection, many of which were deemed to be at least possibly related to infliximab treatment. The serious infections included sepsis, pneumonia, cellulitis, and an intra-abdominal abscess. Similarly, Ljung et al from Sweden noted an annual serious infection rate of approximately 2% in patients treated with infliximab.²⁷⁴ These open-label studies were uncontrolled.^{273,274} In contrast, data from the 5000-patient TREAT registry, which contains a comparator group of patients and is large enough to allow multivariate analysis, suggests that any excess of serious infections in infliximab-treated patients is most likely due to increased severity of CD in these patients and the concomitant use of corticosteroids and not due to infliximab itself.²⁷⁵ It should be noted that patients were not randomized in the TREAT registry. Infliximab should not be given to patients with a clinically active infection.

TNF- α plays a central role in the defense of mycobacterial infections; animal studies have shown that TNF- α can prevent the reactivation of latent tuberculosis.²⁷⁶ TNF- α has been shown to be an important agent involved in formation of the granuloma. The rate of tuberculosis in patients treated with infliximab is significantly higher than the expected rate. In addition, the clinical presentation varies, with more common extrapulmonary involvement (>50%) and a disseminating course in 1 in 3 cases. The risk of tuberculosis can be reduced by screening for latent tuberculosis before initiation of infliximab therapy, using prophylactic antituberculous therapy in patients found to have latent tuberculosis, and maintaining a high index of suspicion for tuberculosis in patients treated with infliximab. A skin test (5 Tinne units) of standard purified protein derivative (PPD) tuberculin units injected strictly intradermally is advocated

initially. The skin test should be assessed after 48–72 hours and based on the presence of induration in millimeters. The presence of induration ≥ 5 mm at 48–72 hours should be interpreted as positive and the patient regarded as having latent tuberculosis. Because the patient who is a candidate for infliximab has usually been treated with corticosteroids and immunosuppressive agents already, the PPD result may be falsely negative.²⁷⁷ The skin test should be combined with a comprehensive medical history (eg, exposure or contact with tuberculosis). Patients with a positive skin test result but negative findings on a chest radiograph should begin therapy for latent tuberculosis based on the standard recommendations of the American Thoracic Society (for an immunocompromised host) before the initiation of infliximab therapy.²⁷⁸

The duration of administration of therapy for tuberculosis before beginning administration of infliximab has not been established or investigated; in general, infliximab should be started at least 1 month after antituberculous therapy has begun.²⁷⁶

Infusion reactions. Infusion reactions typically occur during or 1–2 hours after the administration of infliximab. In the ACCENT I study (573 patients), infusion reactions were reported after 106 of 2026 infusions (5%) (in 23/837 cases after placebo [3%]).^{248,249} These reactions included headaches, dizziness, nausea, erythema at the injection site, flushing, fever, chills, chest pain, cough, dyspnea, and pruritus. In 12 cases (0.6%), infusion reactions resulted in withdrawal from the study. Approximately 1 in 1000 infusions results in a serious infusion reaction. The underlying mechanisms are unclear; an immunoglobulin E–mediated type I hypersensitivity reaction is believed to be present in only a very small number of infusion reactions (those with hypotension and bronchospasm). The following observations speak against an allergenic genesis: (1) most reactions disappear at slow infusion rates, (2) a majority of the reactions do not occur until after the first infusion, and (3) infusion reactions do not occur after every infusion. Serum tryptase levels, which are increased as a result of mast cell activation, and serum immunoglobulin E levels, do not change in patients after infusion reactions to infliximab.²⁷⁹

Several clinical studies have demonstrated a correlation between ATI and the occurrence of infusion reactions. In the ACCENT I study, infusion reactions occurred in 42 of 254 infusions (16%) given to patients with ATI but only in 55 of 656 infusions (8%) given to patients without ATI. Baert et al also noted that infusion reactions were several times more likely in patients who had ATI.²⁵¹ Farrell et al investigated 53 patients treated

episodically with infliximab and found ATI in 19 (36%).²⁵³ All patients with infusion reactions (7/53) had detectable ATI. In this study, the use of hydrocortisone premedication (200 mg IV administered before infusion) reduced the incidence of ATI but not the incidence of infusion reactions. It is clear that while ATI do not explain all infusion reactions, patients with ATI are 2–3 times more likely to develop an infusion reaction during a given infusion. Therefore, an important strategy in preventing infusion reactions is preventing the development of ATI. In this regard, scheduled maintenance therapy every 8 weeks and the concomitant use of immunomodulators are 2 options that seem to be effective.^{248,251} When infusion reactions do occur, mild to moderate reactions often can be controlled just by slowing or temporarily stopping the infusion and by giving acetaminophen 1000 mg orally and diphenhydramine 50 mg orally or IV. A more detailed algorithm for the management of infusion reactions and prophylaxis against further infusion reactions can also be found in well-done studies in the published literature.²⁷⁹ Prophylaxis with corticosteroids, acetaminophen, and diphenhydramine is of unproved benefit in preventing infusion reactions in patients who have not had a previous infusion reaction.

Delayed hypersensitivity-like reactions (serum sickness-like disorder). Delayed infusion reactions typically occur 3–14 days after infliximab infusions. The clinical presentation includes myalgias, arthralgias, fever, rash, pruritus, dysphagia, urticaria, and headaches and is similar in clinical presentation to a serum sickness disorder. These symptoms generally abate spontaneously or occasionally require a brief course of corticosteroids. Serum complement levels are within normal range. It is clear that the principal risk factor for these reactions is a long hiatus between infliximab treatments. In early studies with very long intervals between infliximab infusions (several years), such reactions occurred in almost 25% of patients; the initial administration at weeks 0, 2, and 6, as well as concomitant immunosuppressive therapy, appear to reduce the rate of these reactions. In the ACCENT I study, the same side effects occurred in 2% of patients²⁴⁸; in a retrospective review, Colombel et al observed a serum sickness-like disorder in 1% of patients.²⁷³ Individuals who experience this constellation of symptoms should be evaluated for this side effect. In some cases, subsequent infliximab infusions may be successfully administered with corticosteroid treatment both before and after the infusion. One strategy is to give prednisone 40 mg by mouth or methylprednisolone 100 mg IV 30 minutes before the infusion of infliximab.²⁸⁰ If symptoms recur despite this treatment, infliximab must be discontinued.

Development of autoantibodies and drug-induced lupus reactions. A large percentage of patients with CD (approximately 40%) develop a positive antinuclear antibody while undergoing treatment with infliximab, and 15% of patients will develop antibodies to double-stranded DNA (anti-dsDNA antibodies). This phenomenon has been noted with similar frequency with other anti-TNF agents, and the mechanism underlying it is unknown.²⁸¹ Fortunately, despite the relatively common development of autoantibodies, the development of symptomatic disease (ie, drug-induced lupus) is distinctly unusual. In clinical studies, the development of drug-induced lupus has occurred in far less than 1% of patients and has generally been characterized by arthritis and serositis that resolves promptly on discontinuation of infliximab. No patient has developed renal or central nervous system involvement.²⁸¹ Similarly, Vermeire et al noted that only 2 of 71 patients with positive antinuclear antibodies developed a lupus-like syndrome with polyarthralgias, myalgias, and a typical butterfly rash; after discontinuation of infliximab, the symptoms disappeared.²⁸¹ A diagnosis of drug-induced lupus should be considered when evaluating patients with suspected delayed infusion reactions because some of the symptoms overlap.²⁸²

Malignancy and lymphoproliferative disorder. There does not appear to be any evidence that the use of infliximab increases a patient's risk of developing a solid tumor malignancy (eg, carcinoma). Patients with longstanding CD and treatment with immunosuppressives may be more prone to develop lymphomas,^{283–288} and there may be an increased risk of lymphoma with infliximab as well.²⁸⁹ In the ACCENT I study, out of 580 patients, 3 patients developed solid tumor malignancies (renal, breast, and bladder), 2 patients developed non-melanoma skin cancer, and 1 patient developed lymphoma. The overall rate of cancer in the ACCENT I study was not higher than would be expected in the background population.²⁴⁸ In March 2003, the Arthritis Advisory Committee of the FDA noted an 8-fold higher rate of lymphoma in patients with CD treated with infliximab in clinical trials as compared with the age-, sex-, and race-matched general population (ie, this was not a comparison to a population of patients with CD).²⁸⁹ The risk was based on the occurrence of 2 cases of lymphoma in CD among 1106 patients with CD observed for 1646 patient-years.²⁸⁹ In the 5000-patient TREAT registry, the malignancy rate in infliximab-treated patients has been the same as in patients with CD receiving other treatments only, but the average follow-up in this registry was only approximately 2 years²⁹⁰

and data from the registry are subject to selection and ascertainment bias.

In view of these data, the risk of lymphoma should be discussed with patients with CD before starting treatment with infliximab, as should also be done before starting treatment with 6-MP, AZA, or methotrexate.

Mortality. Multiple studies have shown that the annual mortality rate in patients with CD is between 1.0% and 1.5%, compared with 0.8% in the general US population.^{291–294} The annual mortality rates in the ACCENT I and ACCENT II studies were 0.7% and 0%, respectively.^{248,258} Colombel et al noted an annual mortality rate of 1.3% among 500 patients treated at the Mayo Clinic,²⁷³ whereas Ljung et al from Stockholm County noted the highest reported mortality with infliximab with a rate over 2 years of 2.8% in 217 patients.²⁷⁴ The mortality rate in the TREAT registry in infliximab-treated patients has been the same as in patients with CD not treated with infliximab,²⁷⁵ although the selective enrollment in the registry makes it difficult to interpret the comparison. There did, however, appear to be a significantly increased mortality rate associated with the use of corticosteroids in the TREAT registry.²⁷⁵

Recommendations for infliximab use. *Dose.* The recommended initial dose of infliximab for all IBD indications is 5 mg/kg body wt administered by IV infusion over 2 hours in an induction regimen at weeks 0, 2, and 6. This should be followed by maintenance therapy every 8 weeks in patients who respond. For patients with CD who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. The treatment should be administered under the supervision and control of a specialized health care deliverer, with emergency equipment for severe infusion reactions available. Patients should be monitored for immediate adverse reactions for up to 1 hour after an infliximab infusion.

Treatment of moderately to severely active CD and UC in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (Grade A). Individuals who are resistant to medical therapy (complete and adequate therapy with a corticosteroid or an immunosuppressive agent) or patients who cannot receive such therapies due to intolerance to medications (corticosteroids or medical contraindications (therapy intolerant):

- For induction therapy, the administration of infliximab at time 0, 2, and 6 weeks is recommended; in the case of nonresponse to 3 infusions, further treatment with infliximab is not recommended. (Grade A)

- Withdrawal or tapering of concomitant corticosteroid therapy: if a patient is treated with infliximab and achieves remission, an attempt to withdraw or taper any concomitant corticosteroid therapy is appropriate. (Grade B)
- Treatment with corticosteroids, AZA, 6-MP, or methotrexate before and concomitantly with infliximab can reduce the formation of ATI. (Grade B)

In maintenance therapy, if there is an initial response to infliximab (Grade A). Scheduled maintenance administration of infliximab at 8-week intervals is superior to episodic therapy in several clinical end points; lower ATI rates, fewer hospital stays, and fewer operations speak in favor of regular administration of infliximab, especially in patients who cannot receive concomitant immunosuppressive therapy due to intolerance. In episodic infliximab therapy, premedication with corticosteroids appears to be beneficial.^{253,295} This can be provided with hydrocortisone 200 mg IV on the same day as infliximab²⁵³ administration, or alternatively oral prednisone can be administered the day before infliximab therapy. In terms of toxicity, there are no significant differences between maintenance and episodic therapy. In the case of a loss of effect of infliximab in terms of a clinical exacerbation during regular 8-week administration, the intervals between doses should be shortened in accordance with the authorization for 5 mg/kg. Shortening the intervals to less than 4 weeks is not recommended. If a patient with CD does not receive benefit with a change in medication-dosing frequency (with a maximum frequency of every 4 weeks), an increase in dose by 5 mg/kg (to 10 mg/kg daily) could be considered.

Treatment of CD with fistulas in patients who have not responded despite complete and adequate therapy with conventional treatments (including antibiotics, surgical drainage with examination under anesthesia, and/or immunosuppressive therapy) (Grade A). An initial infusion of infliximab at a dose of 5 mg/kg is followed by subsequent infusions of infliximab at 5 mg/kg at weeks 2 and 6. If the patient does not have a response to the induction regimen, infliximab should be discontinued. However, patients achieving fistula response should receive scheduled maintenance therapy every 8 weeks with 5 mg/kg. In the case of a loss of effect of infliximab in terms of a clinical exacerbation during regular 8-week administration, the intervals between doses should be shortened in accordance with the authorization for 5 mg/kg. Shortening the intervals to less than 4 weeks is not recommended. If an individual does not receive benefit with a change in medication-dosing frequency (with a maximum frequency of every 4 weeks), an increase in the dose by 5

mg/kg (to 10 mg/kg daily) could be considered. There are no controlled data beyond 1 year, but magnetic resonance imaging studies have demonstrated persistence of the fistula track, and patients will be at high risk for recurrence if treatment with infliximab is discontinued.

Before the administration of infliximab, delineation of the fistula anatomy is useful (clinical examination, typically with an examination under anesthesia, endosonography, or magnetic resonance imaging) to exclude the presence of an abscess.²⁹⁵ Abscesses should be drained adequately before treatment with infliximab. Seton drains should remain in place at least until after the second infusion of infliximab.²⁹⁶

Extraintestinal manifestations. Extraintestinal manifestations are not included in the approved indications for use of infliximab; however, there have been numerous case reports and case series that strongly suggest effectiveness. Infliximab is suitable for the treatment of therapy-resistant extraintestinal manifestations of CD (Grade C). Several areas that have been reported include pyoderma gangrenosum,²⁹⁷ erythema nodosum,²⁹⁸ metastatic CD,²⁹⁹ uveitis,³⁰⁰ episcleritis,³⁰¹ axial arthropathy,³⁰² peripheral arthropathy,³⁰³ aphthous stomatitis,³⁰⁴ and pulmonary CD.³⁰⁵

Contraindications. Infliximab is contraindicated in patients with active tuberculosis and other serious infections, such as sepsis, undrained abscess, and opportunistic infections, such as herpes zoster, cytomegalovirus, or *P. carinii*. In patients with moderate to severe congestive heart failure (New York Heart Association Class III or Class IV), infliximab should not be administered because an increased mortality when compared with controls has been reported in this patient population.³⁰⁶ Individuals with known hypersensitivity to infliximab or other murine proteins should avoid exposure to infliximab. It is generally not advocated that infliximab should be given to patients with known or suspected demyelinating disorders,^{230–232,307–309} optic neuritis,^{310,311} or recent malignant tumors and lymphomas.³¹²

Conclusions

Although there are evidence-based data to support the use of corticosteroids, immunomodulators, and infliximab in the treatment of patients with IBD, there are many aspects of therapy with these agents for which the data are lacking or inadequate. Additional prospective data are needed to resolve the areas of controversy. The gastroenterologist who uses these agents must have a clear understanding of the proven benefits and risks of these therapies to provide optimal care to the patient with IBD.^{313–315}

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