Subject Review

Maintenance of Symptomatic Remission in Patients With Crohn's Disease

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Crohn's disease is a chronic inflammatory intestinal disorder characterized in most patients by repeated episodes of diminished and exacerbated symptoms. Recent controlled trials demonstrated that oral preparations of 5-aminosalicylic acid decrease recurrence rates by approximately 40% when administered long-term to patients with quiescent Crohn's disease. Orally administered corticosteroids, sulfasalazine, metronidazole, azathioprine, and cyclosporine have not proved of benefit in the prevention of recurrences of Crohn's disease. Nonetheless, corticosteroids, metronidazole, and azathioprine can control chronically active disease. Methotrexate may have some benefit in the treatment of active Crohn's disease, but its role in maintenance of remission has not been investigated. Elimination diets seem to prolong periods of symptomatic remission. Further studies are needed to define subgroups of patients who are most likely to benefit from preventive therapy.

Of patients with Crohn's disease who have not previously undergone surgical treatment and who are in symptomatic remission, 25 to 50% will experience symptomatic recurrences after 1 year, and 40 to 65% will have recurrences by 2 years.[1,2] Of patients who have undergone surgical resection of intestinal segments involved with Crohn's disease, 30 to 50% will have symptomatic recurrences during the first 5 postoperative years, and 50 to 80% will have symptomatic recurrences by 10 years postoperatively.[3] Increasing the length of the margins of normal intestine removed at the time of resection does not decrease the frequency of recurrent disease.[3-7] Because of the high rate of recurrence, a safe and effective regimen has long been sought for maintaining remission in patients with Crohn's disease.

MAINTENANCE THERAPY

Study Designs.—More than 30 clinical trials have examined the role of medical therapy in the prevention of recurrent Crohn's disease that has become inactive spontaneously after medical therapy or surgical resection. Several problems complicate the interpretation and application of these data to clinical practice.

First, definitions of recurrence and remission vary among studies. Clinical or symptom-related definitions of recurrence are based on a scoring system such as the Crohn's Disease Activity Index,[8] in which eight factors are used to obtain an overall clinical rating of disease activity. With use of the Crohn's Disease Activity Index, remission is usually defined as a score of less than 150 and relapse as a score of more than 150 in conjunction with a more than 100-point increase over the initial score.[9] In some clinical trials, endoscopic, pathologic, or surgical data are used to determine recurrence or remission, and the criteria are not standardized.[10-12] Crude recurrence rates (percentage of all patients in whom Crohn's disease has redeveloped, regardless of duration of follow-up) may be misleading because the actual recurrence rate is often underestimated. Actuarial or life-table analysis of cumulative recurrence rates is an appropriate method for studying Crohn's disease. In order to account for the variable times to recurrence and the varied durations of follow-up, the cumulative recurrence rate is calculated for each year of follow-up on the basis of the number of patients at risk for recurrence that year.[13,14]

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Second, definitions of disease activity are imprecise. In most studies, "maintenance of remission" refers to therapy for preventing symptomatic recurrence in patients who are already asymptomatic and who are not receiving treatment.[9] In some studies, however, maintenance of remission refers to medical therapy that induces active disease into symptomatic remission and then is continued indefinitely.[15] The latter approach is actually long-term suppression of active disease. This distinction is important because treatments that suppress chronic disease activity are not necessarily effective in maintenance of remission. For example, corticosteroids can control active disease, but they have no proven benefit in preventing recurrence in patients in remission.[1,2,16]

Third, enlisting a homogeneous group of patients for study is difficult because of the variability in the anatomic sites of bowel involvement, the clinical course, and prior therapy. For example, the National Cooperative Crohn's Disease Study and the European Cooperative Crohn's Disease Study included patients with prior disease at any site, those with quiescent disease who had not undergone surgical intervention, and those with quiescent disease after resection of all diseased bowel.[1,2] For each of these factors, patients should be randomly assigned or stratified into comparable treatment and placebo groups. In addition, the results of studies in patients with quiescent disease after resection, such as the Inter-Nordic Cooperative Study,[17] may be inapplicable to patients with medically induced or spontaneous remission.

Fourth, the risk of a type II statistical error has plagued many studies of remission maintenance in patients with Crohn's disease. For instance, Crohn's disease may remain asymptomatic for years without treatment; therefore, even in studies that have a follow-up period of at least 1 year, a risk exists of not detecting therapeutic benefit in comparison with placebo. The problem can be worse in studies of only 6 months or less.[12,18] Because relapse rates in patients with Crohn's disease may be as low as 25% at 1 year, studies should be designed with sufficient numbers of patients to detect a difference in outcome. Unfortunately, some studies have had small numbers or high dropout rates (or both).[10,17,19]

Randomized Controlled Trials. **Corticosteroids.**—In four controlled trials, each of 2 to 3 years' duration (Table 1), long-term low-dose corticosteroid therapy, in dosages ranging from 7.5 to 15 mg of prednisone daily, was no better than placebo in preventing recurrence of Crohn's disease.[1,2,16,20] In one of these trials, prednisolone was administered in combination with sulfasalazine; however, this was not an actual maintenance study because patients were treated for only 8 months but underwent follow-up for 3 years for relapse.[20] In the one controlled trial that had positive results, 18 patients with quiescent Crohn's disease, considered at high risk for symptomatic recurrence on the basis of increased laboratory markers of inflammation, were randomly assigned to receive methylprednisolone (0.25 mg/kg daily) or placebo.[18] This small group of patients was observed for only 6 months, and the relapse rate was lower with use of corticosteroids than with placebo. Nevertheless, the weight of evidence from these four trials supports the conclusion that corticosteroids do not have a major benefit in the prevention of recurrences of Crohn's disease.

Table 1.—**Placebo-Controlled Trials of Corticosteroids to Prevent Recurrent Crohn's Disease***

Reference	Agent (dosage)	No. of patients	Type of remission	Site of prior disease	Relapse (definition)	Duration of trial (mo)	Relapse rate, corticosteroid vs placebo (*P* value)
Positive results							
Brignola et al[18]	Methylprednisolone (0.25 mg/kg/day)	18	M	SB, SB + C, C	Clinical	6	6 mo, 11% vs 78% (<0.001)
Negative results							
Bergman & Krause[20]	Prednisolone (15 mg/day for 2 wk, 10 mg/day for 14 wk, 5 mg/day for 17 wk) with sulfasalazine	97	S	SB, I, IC, C, IC + R	Radiologic	8 (Rx); 36 (FU)	12 mo, 14% vs 11% (NS) 24 mo, 36% vs 26% (NS) 36 mo, 47% vs 37% (NS)
Smith et al[16]	Prednisone (7.5 mg/day)	64	S, M	SB, SB + C, C	Clinical	36	12 mo, 0% vs 10% (NS) 24 mo, 20% vs 17% (NS) 36 mo, 28% vs 31% (NS)
Summers et al[1] (NCCDS)	Prednisone (0.25 mg/kg/day)	274	S, M	SB, SB + C, C	Clinical	24	12 mo, 28% vs 28% (NS) 24 mo, 31% vs 40% (NS)
Malchow et al[2] (ECCDS)	Methylprednisolone (8 mg/day)	237	S, M	SB, SB + C, C	Clinical	24	12 mo, 38% vs 51% (NS) 24 mo, 53% vs 66% (NS)

*C = colon; ECCDS = European Cooperative Crohn's Disease Study; FU = follow-up; I = ileum; IC = ileocolic area; M = medical remission; NCCDS = National Cooperative Crohn's Disease Study; NS = not significant; R = rectum; Rx = treatment; S = postsurgical remission; SB = small bowel.

Sulfasalazine.—Sulfasalazine, a 5-aminosalicylic acid (5-ASA) linked by an azo bond to sulfapyridine, has been studied in six randomized trials in patients with Crohn's disease in remission. The trials lasted 8 months to 3 years (Table 2),[1,2,10,17,19,20] and the dosages of sulfasalazine ranged from 1.5 to 3.0 g daily. Three of the studies included only patients who had undergone resection;[10,17,20] the other three studies included patients who either had undergone surgical treatment or were in medical remission.[1,2,19] In five of these trials, sulfasalazine was found no more effective than placebo in preventing symptomatic recurrences.[1,2,17,19,20] Two of these five studies may have had an insufficient number of patients to detect a therapeutic effect,[17,19] and one was not an actual maintenance study because patients were treated for only 8 months but underwent follow-up for 3 years for relapse.[20] Two of the studies that showed no benefit, the National Cooperative Crohn's Disease Study and the European Cooperative Crohn's Disease Study, had large sample sizes, but only modest dosages of sulfasalazine (0.5 g per 15 kg daily and 3.0 g daily, respectively) were administered.[1,2] These dosages of sulfasalazine may have been inadequate because experience in noncontrolled trials suggests that full therapeutic dosages of up to 4 g/day may be necessary for maintenance treatment of Crohn's disease.[21] The one study that showed some benefit was a German multicenter trial of 232 postoperative patients who were randomly assigned to receive sulfasalazine (3 g/day) or placebo for a 3-year period.[10] The recurrence rate was significantly lower in the sulfasalazine-treated patients after 1 and 2 years, but by the third year, statistically significant differences were not detectable. After the third year, however, only 44 patients remained in the trial, and perhaps a type II statistical error existed. Despite the somewhat encouraging results from this last-mentioned study, sulfasalazine does not seem to prevent Crohn's disease from recurring.

Oral Preparations of 5-ASA.—New oral preparations of 5-ASA, also called mesalamine in North America and mesalazine in Europe, may be effective in preventing recurrences of Crohn's disease (Tables 3 and 4). These drugs release 5-ASA into the small intestine or colon. Three 5-ASA oral preparations, Asacol, Claversal (also marketed as Salofalk), and Pentasa, have been evaluated in randomized controlled trials as maintenance therapy for Crohn's disease. The properties of the enteric coating of these agents are listed in Table 3.

In the International Mesalazine Study Group, 248 patients with inactive Crohn's disease were randomly assigned to receive Claversal (1.5 g/day) or placebo for a 12-month period.[22] This study included patients with inactive disease after surgical or medical therapy and with various sites of prior disease activity. Some patients had received up to 2.5 mg/day of prednisone on entry into the study, and other patients had discontinued use of sulfasalazine during the month before entry; thus, whether some patients were in actual remission or had active disease controlled by corticosteroids or sulfasalazine is unclear. Remission and relapse were determined clinically on the basis of the Crohn's Disease Activity Index score. A few side effects such as diarrhea, constipation, and nausea were encountered, but none was serious. Of the 209 patients who completed the study, the cumulative life-table relapse rate was significantly lower in patients treated with 5-ASA in comparison with those who received placebo (22.4% versus 36.2%). This outcome represented a 38% decrease in the possibility of a recurrence. Although subgroups were not stratified before randomization, the relapse rate was lower with use of 5-ASA

Table 2.—**Placebo-Controlled Trials of Sulfasalazine to Prevent Recurrent Crohn's Disease***

Reference	Dosage	No. of patients	Type of remission	Site of prior disease	Relapse (definition)	Duration of trial (mo)	Relapse rate, sulfasalazine vs placebo (*P* value)
Positive results							
Ewe et al[10]	3 g/day	232	S	I, IC, C	Radiologic Endoscopic Pathologic	36	1 yr, 16% vs 28% (<0.01) 2 yr, 24% vs 38% (<0.01) 3 yr, 38% vs 38% (NS)
Negative results							
Bergman & Krause[20]	3 g/day for 16 wk, 1.5 g/day for 17 wk (with prednisolone)	97	S	SB, I, IC, C, IC + R	Radiologic	8 (Rx); 36 (FU)	12 mo, 14% vs 11% (NS) 24 mo, 36% vs 26% (NS) 36 mo, 47% vs 37% (NS)
Multicentre Trial[19]	3 g/day	43	S, M	SB, IC, C	Clinical	12	12 mo, 34% vs 13% (NS)
Wenckert et al[17]	3 g/day	66	S	SB, I, IC, C	Clinical	18	12 mo, 13% vs 15% (NS) 18 mo, 13% vs 45% (NS)
Summers et al[1] (NCCDS)	0.5 g/15 kg/day	274	S, M	SB, SB + C, C	Clinical	24	12 mo, 32% vs 28% (NS) 24 mo, 40% vs 40% (NS)
Malchow et al[2] (ECCDS)	3 g/day	237	S, M	SB, SB + C, C	Clinical	24	12 mo, 45% vs 51% (NS) 24 mo, 61% vs 66% (NS)

*For explanations of abbreviations, see Table 1.

Table 3.—**Oral Preparations of 5-Aminosalicylic Acid (Mesalamine) Studied as Maintenance Therapy for Crohn's Disease***

Proprietary name	Coating and properties	Site of release
Asacol	Eudragit-S-coated capsules dissolve to release 5-ASA in pH >7.0	Terminal ileum and colon
Claversal or Salofalk	Eudragit-L-coated capsules dissolve to release 5-ASA in pH ≥5.6	Distal jejunum, ileum, and colon
Pentasa	Ethyl cellulose-coated 5-ASA microgranules slowly dissolve throughout bowel	Proximal jejunum and throughout small bowel and colon

*5-ASA = 5-aminosalicylic acid.
Data from Martin F. Oral 5-ASA preparations. In: Bayless TM, editor. Current Management of Inflammatory Bowel Disease. Toronto: Decker, 1989: 72-77.

in patients with prior ileal disease (8.3% versus 31.0%) and in those with prior bowel resections (14.2% versus 47.0%). The benefit of 5-ASA in subgroups of patients with prior colitis or ileocolitis was less apparent.

In the Italian Inflammatory Bowel Disease Study Group, 125 patients with inactive Crohn's disease were randomly assigned to receive Asacol (2.4 g/day) or placebo for a 12-month period.[9] This study included patients who had undergone prior resection only if they had a documented recurrence of disease postoperatively. Patients could have had prior ileitis, ileocolitis, or colitis but not disease of the proximal small intestine. These patients were in clinical remission, as indicated by the fact that none had taken any medication for Crohn's disease for at least 3 months before entry into the study. Side effects of Asacol were rare and minor. Remission and relapse were determined on the basis of the Crohn's Disease Activity Index score. The cumulative life-table relapse rate was significantly lower for 5-ASA-treated patients in comparison with placebo-treated patients (34% versus 55%); the possibility of a recurrence was decreased by 38%. Although subgroups were not stratified before randomization, the relapse rate was lower with use of 5-ASA in comparison with placebo in patients with ileal disease (26% versus 57%), in those with prior bowel resection (9% versus 58%), and in those in prolonged remission before entry into the study (19% versus 56%). The benefit of 5-ASA in subgroups of patients with colitis or ileocolitis was less apparent in this study also.

A French multicenter trial compared Pentasa (2 g/day) with placebo in 161 patients in remission during a 2-year period.[23] Patients with prior disease activity at various sites and with inactive disease after surgical or medical therapy were included. Remission and relapse were determined on the basis of the Crohn's Disease Activity Index score. For the stratum of patients who were in remission less than 3 months when Pentasa therapy was initiated, the clinical relapse rate was significantly less with 5-ASA in comparison with placebo at both 1 year (28% versus 68%) and 2 years

Table 4.—**Placebo-Controlled Trials of Preparations of 5-Aminosalicylic Acid to Prevent Recurrent Crohn's Disease***

Reference	Agent (dosage)	No. of patients	Type of remission	Site of prior disease	Relapse (definition)	Duration of trial (mo)	Relapse rate, 5-ASA vs placebo (*P* value)
Positive results							
Thomson et al[22]	Claversal (1.5 g/day)	209	S, M	I, IC, C	Clinical	12	12 mo, 22.4% vs 36.2% (0.0395)
Prantera et al[9]	Asacol (2.4 g/day)	125	M	I, IC, C	Clinical	12	12 mo, 34% vs 55% (0.02)
Gendre et al[23]	Pentasa (2 g/day)	161	S, M	SB, SB + C, C	Clinical	24	12 mo, 28% vs 68% (<0.05) 24 mo, 55% vs 71% (<0.05)
Caprilli et al[11]	Asacol (2.4 g/day)	83	S	I, IC	Endoscopic	12	12 mo, 7-34% vs 38-70% (<0.01)
Negative results							
Brignola et al[24]	Pentasa (2 g/day)	44	M	I, IC, C	Clinical	4	4 mo, 42.4% vs 59% (NS)
Fiasse et al[25]	Claversal (1.5 g/day)	62	S	I, IC	Clinical	12	12 mo, 54% vs 37% (NS)
Florent et al[12]	Claversal (1.5 g/day)	126	S	I, IC, C	Endoscopic	3	3 mo, 50% vs 63% (NS)

*5-ASA = 5-aminosalicylic acid. For explanations of other abbreviations, see Table 1. See text for discussion of subgroups with benefit.

(55% versus 71%). Patients who had been in remission from 3 to 24 months at the time of entry into the study received no therapeutic benefit.

When the Italian Study Group of the Colon compared Asacol (2.4 g/day) with placebo in 83 patients with quiescent disease after resection of the affected area of the ileum or of the ileum and colon, they found that the endoscopic recurrence rate at 6 and 12 months was significantly lower with 5-ASA.[11] A preliminary report suggests that Eudragit-coated 4-aminosalicylic acid may be as effective as coated 5-ASA in the maintenance treatment of Crohn's disease.[26]

Success with oral preparations of 5-ASA has not been universal. Brignola and associates[24] randomly assigned 44 patients with inactive Crohn's disease at high risk for recurrence to receive Pentasa (2 g/day) or placebo for 4 months. No significant difference was noted in the clinical relapse rate of the 5-ASA- and placebo-treated patients overall, but of 19 patients who had only ileal disease, the clinical relapse rate was less with 5-ASA than with placebo (30% versus 67%). In a Belgian trial that compared Eudragit-L-coated 5-ASA (1.5 g/day) with placebo in 62 patients with inactive disease after resection, no difference was noted in the clinical relapse rate at 12 months.[25] In another trial of Eudragit-L-coated 5-ASA (Claversal, 1.5 g/day) versus placebo in 126 patients with inactive disease after resection, no significant difference was noted in the endoscopic relapse rate at 3 months.[12]

Azathioprine and 6-Mercaptopurine.—In a randomized controlled trial, 6-mercaptopurine, the active metabolite of azathioprine, proved effective in the treatment of active Crohn's disease.[27] Extensive experience in noncontrolled studies suggests that, in patients whose disease responds to 6-mercaptopurine or azathioprine therapy, continued treatment can maintain an asymptomatic state.[28-31] The National Cooperative Crohn's Disease Study is the only controlled trial that has examined the efficacy of azathioprine in preventing recurrence in patients with asymptomatic disease who were not receiving other therapy.[1] In comparison with placebo, azathioprine had no benefit during the 2-year treatment period. The 1 mg/kg daily dosage of azathioprine may have been too low, however. Other controlled trials have shown that higher doses are effective in maintaining an asymptomatic state in patients with active disease that has been controlled with corticosteroids or azathioprine.[32-34] For example, when O'Donoghue and colleagues[32] randomly assigned 51 patients who were in azathioprine-induced remission to continue azathioprine therapy (2 mg/kg per day) for 12 months or to discontinue it, they found that the relapse rate at 1 year was lower with azathioprine (5% versus 41%). Willoughby and coworkers[33] randomly assigned 22 patients who were in remission induced by azathioprine and prednisolone to receive azathioprine (2 mg/kg per day) or placebo for a 6-month period and found a lower relapse rate with azathioprine (9% versus 73%; $P<0.01$). A similar study of 20 patients with active disease controlled with use of corticosteroids found a 20% relapse rate with azathioprine at 6 months in comparison with a 50% relapse rate with placebo.[34] Azathioprine and 6-mercaptopurine have the potential for serious complications in up to 10% of patients; thus, hematology values must be monitored periodically.[32,35] Another drawback of their long-term use is concern of potential teratogenic effects.[36] Although some evidence suggests that azathioprine and 6-mercaptopurine therapy are safe during pregnancy,[37,38] the available information is limited; thus, discontinuing or avoiding use of these agents in men and women who are planning conception is advisable.

Cyclosporine.—In a randomized controlled trial, cyclosporine was shown to have benefit for patients with active Crohn's disease during a 6-month treatment period; however, no difference was noted in the number of patients in sustained remission 6 months after cyclosporine therapy was discontinued.[39,40] Results of noncontrolled trials suggest that continuous cyclosporine therapy is associated with sustained remission for as long as 3 years in some patients.[41,42] Other patients have experienced relapse during prolonged cyclosporine therapy, and in some patients, such treatment had to be discontinued because of serious side effects such as nephrotoxicity.[43-45] In one open trial, 14 patients with active disease who were receiving 5 mg/kg of cyclosporine daily entered into remission.[43] The drug was then decreased by 1 mg/kg at 2-month intervals until a maintenance dose of 2 mg/kg was attained. Of 14 patients, 12 (86%) had a relapse between 8 and 36 weeks of the study despite cyclosporine maintenance. Relapse occurred in seven patients when the dosage of cyclosporine reached 2 mg/kg, in three at 3 mg/kg, in one at 4 mg/kg, and in one at 5 mg/kg. The Canadian Crohn's Relapse Prevention Trial compared the efficacy of low-dose cyclosporine therapy during an 18-month period in 305 patients with Crohn's disease.[46] The mean dosage of cyclosporine was 4.8 mg/kg per day, and the mean cyclosporine level by whole blood radioimmunoassay was 200 ng/ml. At these low doses, cyclosporine therapy was no better than placebo. The results of these noncontrolled and controlled studies do not support the use of low-dose cyclosporine therapy to maintain remission in patients with Crohn's disease.

Methotrexate.—Data from noncontrolled studies suggest that most patients with active disease that responds immediately to methotrexate therapy will be in remission for many months with continued use of methotrexate.[47] In a placebo-controlled trial, methotrexate decreased the number of exacerbations in 33 patients with corticosteroid-dependent Crohn's disease; however, major side effects were noted in 23% of patients who received methotrexate.[48] Two

multicenter studies that are evaluating the efficacy of methotrexate in patients with chronically active Crohn's disease are in progress. To date, no published reports have described the use of methotrexate to prevent recurrences of active Crohn's disease.

Antibiotics.—In a placebo-controlled trial of 60 patients with Crohn's ileitis who had undergone resection of the terminal ileum, those treated with metronidazole had less severe endoscopic changes in the neoterminal ileum than did those who received placebo; however, no overall clinical benefit could be demonstrated.[49] In an open trial of rifabutin and ethambutol in 10 patients with asymptomatic endoscopic recurrence in the neoterminal ileum after resection of the ileum, symptoms of active Crohn's disease developed in all but one patient during the next year despite therapy.[50]

Dietary Therapy.—Several controlled trials indicate that an elemental diet can induce remission in patients with active Crohn's disease, but none has demonstrated that an elemental diet can maintain long-term remission.[51-55] Although preliminary reports of two controlled studies show that an elemental diet is as effective as corticosteroids in managing active Crohn's disease, relapses occur more frequently and earlier after treatment with an elemental diet than after corticosteroid therapy.[56,57] Evidence from controlled trials demonstrates that the detection and exclusion of specific irritating foods may prolong a remission induced by bowel rest and nutritional therapy. In one trial, 20 patients with Crohn's disease in remission after consumption of only an elemental diet or total parenteral nutrition were randomly assigned to receive either a high-carbohydrate fiber diet or an exclusion diet in which one new food was introduced each day, and any food that precipitated symptoms was then avoided.[58] Of the 10 patients who received the exclusion diet, 7 remained in remission for 6 months in comparison with none of those who received the high-carbohydrate fiber-rich diet ($P<0.05$). In a multicenter trial of 78 patients with active Crohn's disease, remission was achieved with an elemental diet, and then the patients were randomly assigned to either a 3-month course of corticosteroids or an exclusion diet.[59] After 2 years, only 26% of the corticosteroid-treated group were in remission in comparison with 53% of those who received the exclusion diet ($P<0.05$).

Vitamin A, in a dosage of 50,000 U twice daily, was ineffective in a placebo-controlled trial for preventing relapse of Crohn's disease.[60]

Future Strategies. **Novel Drugs.**—Any agent that proves safe and effective in the treatment of active Crohn's disease should be tested for efficacy as long-term maintenance therapy. Potential drugs for further study include budesonide, a potent corticosteroid with few systemic effects,[61] leukotriene B_4 inhibitors,[62] and interleukin 1 antagonists.

Nonpharmacologic Immunomodulation.—Preoperative blood transfusions may decrease the recurrence rates of Crohn's disease after resection, perhaps through immunomodulation.[63,64] Lymphocyte apheresis may induce prolonged remissions in patients with Crohn's disease.[65] Although apheresis is unlikely as a first-line approach to prevent recurrent Crohn's disease because of cost and technical requirements, increased understanding of the immune system may allow selective and safe immunomodulation. For instance, perhaps cytokines or monoclonal antibodies could be used to prevent recurrent Crohn's disease.

Prediction of Potential for Relapse.—Various laboratory factors have been studied for their utility in predicting relapses in patients with symptomatically quiescent Crohn's disease.[18,66-68] For example, in a retrospective study, Wright and associates[67] demonstrated that abnormalities of serum orosomucoid and α_1-antitrypsin preceded symptomatic recurrence by 1 to 3 months. In a similar retrospective study, Brignola and colleagues[66] compiled a prognostic index using erythrocyte sedimentation rate, acid α_2-glycoprotein, and α_2-globulin that predicted 88% of those who experienced relapse. Thus far, a prospective study of the predictive value of these factors has not been reported.

Rutgeerts and coworkers[69] performed ileocolonoscopy in 89 patients within 1 year after resection of the ileocecum for Crohn's disease to determine the presence and severity of lesions in the neoterminal ileum. During clinical follow-up throughout the next 5 years, patients with diffuse endoscopic lesions experienced early symptomatic recurrence and complications, even though most were asymptomatic at the time of the initial postsurgical examination. Patients with no lesions or mild endoscopic lesions had a low symptomatic recurrence rate and an uneventful course. Thus, endoscopic assessment seems effective for selecting patients at high risk for symptomatic recurrence. In addition, endoscopic relapse has proved a useful model for detecting a benefit of maintenance therapy for Crohn's disease, as demonstrated in the previously discussed study of metronidazole as preventive therapy after resection.[49]

CONCLUSION

Eventually, most patients have symptomatic recurrences of Crohn's disease after surgical resection, spontaneous remission, or medication-induced remission. Evidence from randomized controlled trials indicates that low-dose corticosteroid therapy, sulfasalazine, and cyclosporine have no major effect in preventing recurrent Crohn's disease. Azathioprine and 6-mercaptopurine effectively suppress chronic disease activity and maintain medication-induced remission, but the potential risks of side effects may outweigh the benefits of continuous treatment to prevent relapse in asymptomatic patients. Limited data from controlled trials indicate that an

elimination diet may maintain symptomatic remission induced by bowel rest and nutritional therapy. The possible benefits of methotrexate and antibiotics in that situation have not been tested.

The results of recent studies in which orally administered 5-ASA agents were used as maintenance therapy for Crohn's disease are encouraging. Four studies demonstrated that orally administered 5-ASA preparations decrease recurrence rates by approximately 40% when administered long-term to patients with inactive Crohn's disease. The benefit seems most apparent in patients with past ileitis and prior resections. In comparison with the benefit of long-term sulfasalazine as preventive therapy for ulcerative colitis (20% relapse rate with sulfasalazine at 1 year versus 70 to 85% with placebo),[70-73] the effect of 5-ASA preparations in the prevention of relapse in Crohn's disease is relatively modest. Nevertheless, this benefit is achieved with minimal risk; these drugs are safe and well tolerated. The encouraging results of these recent studies should be discussed with patients who have quiescent Crohn's disease, and the use of orally administered 5-ASA preparations should be seriously considered for maintaining symptomatic remission.

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