# Maintenance therapy for inflammatory bowel disease: What really works

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**LR SUTHERLAND. Maintenance therapy for inflammatory bowel disease: What really works. Can J Gastroenterol 1997; 11(3):261-264.** The propensity of inflammatory bowel disease sufferers to experience recurrent episodes or disease flares is well documented. Until a cure can be found, strategies to lengthen the period of remission offer the greatest opportunity to reduce morbidity and enhance patient quality of life. Therapies that have been shown in randomized, controlled, double-blind clinical trials to either lengthen the time of remission or improve the odds of staying in remission during a set time interval are required.

**Key Words:** *Inflammatory bowel disease, Maintenance therapy, Patient quality of life, Review, Therapy*

## Traitement d'entretien dans la maladie inflammatoire de l'intestin

**RÉSUMÉ :** La propension des personnes atteintes d'une maladie inflammatoire de l'intestin à souffrir d'épisodes récurrents ou de poussées de la maladie est bien documentée. Dans l'attente d'un traitement curatif, les stratégies visant à prolonger les périodes de rémission offrent la meilleure garantie pour réduire la morbidité et améliorer la qualité de vie des patients. Les traitements que des essais cliniques contrôlés, randomisés et à double insu ont révélé efficaces pour allonger la période de rémission ou améliorer les chances de rester en rémission pendant une période de temps fixe doivent être utilisés.

Almost inherent in the definition of inflammatory bowel disease is its propensity for recurrent episodes or disease flares. Until a cure for inflammatory bowel disease can be discovered, strategies to lengthen the period of remission offer the greatest opportunity to reduce morbidity and enhance patient quality of life. The definition as to 'what really works' includes therapies that have been shown in randomized, controlled, double-blind clinical trials to either lengthen the time in remission or improve the odds of staying in remission during a set interval of time (eg, one year).

## ULCERATIVE COLITIS

Early epidemiological studies reported that patients had an 80% chance of a disease flare in the year following treatment of an acute episode of ulcerative colitis (1,2). The concept of maintenance therapy in ulcerative colitis was demonstrated to be of benefit in three trials from the United Kingdom in the early 1960s. Sulfasalazine was the first drug shown to alter annual relapse rates. When the three placebo controlled studies were considered, the risk of a flare was reduced by approximately 75% (90% CI 90-60%) when patients took sulfasalazine (3). The recommended dose of sulfasalazine 2 g/day was based on a study that demonstrated that the slight improvement in relapse rates associated with higher doses of sulfasalazine (4 g/day) was at the expense of a greater prevalence of adverse events (4).

With the introduction of the newer release formulations of mesalamine (5-aminosalicylic acid [5-ASA]), two questions needed to be answered. First, do they work? Three placebo controlled studies confirm their effectiveness in maintaining remission (5-7). Second, are these newer formu-

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*Received for publication August 16, 1996. Accepted August 19, 1996*

lations better than sulfasalazine? Based on comparative trials of sulfasalazine and 5-ASA involving 1359 patients, there is no evidence that mesalamine is superior to sulfasalazine (8). Sulfasalazine patients were more likely to remain in remission compared with those taking mesalamine, but the confidence intervals for this estimation include unity (ie, the difference is not statistically significant). The trials may, however, have overestimated the clinical efficacy of sulfasalazine. Patients intolerant to sulfasalazine were excluded from entering the comparative trials. This selection bias would minimize any differences in side effect profiles between the two drugs. The higher incidence of adverse events might have altered the efficacy, and a stronger case might be made for the newer preparations. The effects of sulfasalazine on spermatogenesis are well known. Male patients with ulcerative colitis who wish to father a child should be switched to one of the newer preparations (9).

Maintenance of remission in patients intolerant to 5-ASA is challenging. It is generally conceded that corticosteroids, effective in the management of flares of ulcerative colitis, are not effective in maintenance of remission, at least when given in low doses (50 mg/day cortisone, 15 mg/day prednisone, 40 mg prednisolone on alternate days) (10-12). Studies of immunosuppressants, such as azathioprine, have had an insufficient sample size to make definitive statements regarding their potential efficacy in maintaining remission, but results of a placebo controlled withdrawal study are encouraging (13). It should be noted, however, that withdrawal studies suffer from a selection bias in that they have already selected a subgroup of patients who have responded to the medication, which favours finding a positive result.

Antibiotics have also been assessed in clinical trials involving only a few patients. In a 12-month pilot study performed in Israel, metronidazole was deemed to be as effective as sulfasalazine in maintaining remission (41% of patients on metronidazole maintained remission compared with 17% on sulfasalazine; difference 24%; 95% CI –3% to 51%)(14) but the possibility of a type II error cannot be dismissed. Lobo and colleagues (15) reported that tobramycin, shown to be useful as adjunctive therapy in acute ulcerative colitis, failed to induce sustained remission.

## CROHN'S DISEASE

Essentially every medication assessed in the management of active Crohn's disease has also been tested for maintenance sustaining properties. Early trials of sulfasalazine were flawed by inadequate sample size and mixtures of patients who differed in terms of disease location and mode of induction of remission (16). The largest trial of sulfasalazine in postoperative patients demonstrated reductions in clinical recurrence over the first two years (17).

Brignola et al (18) recently reported differences in the degree of endoscopic recurrence for mesalamine-treated compared with placebo-treated patients. Three additional studies were reported in 1995. McLeod and associates (19) demonstrated that mesalamine 3.0 g/day, given to patients within eight weeks following resection, was associated with a symptomatic recurrence rate of 31% versus 41% in placebo-treated patients (P=0.031, one-tail test). In another study, 3 g/day mesalamine was found to be no better than placebo in preventing disease recurrence (20). A third study provided equivocal results (21). In 1996, Modigliani and associates (22) reported a large randomized trial evaluating the effect of mesalamine on steroid withdrawal in patients with active disease who maintained remission over the next 12 months. Relapse rates for mesalamine (4 g/day) compared with placebo were similar at the end of the trial. Using advanced statistical techniques mesalamine was shown to be more effective than placebo, but the generalizability of such a manipulation is not yet known.

Results from two meta-analyses (23,24) indicate that mesalamine therapy reduces the odds of a recurrence in the next year by approximately 33% to 50%. Most of the studies included a mixture of postsurgical and medically induced remission patients. Results of meta-analysis should always be interpreted cautiously because they may be subject to publication bias and cannot be substituted for large randomized controlled trials. Also, pharmaceutical companies may suppress negative studies. On the other hand, it is unlikely that there will ever be a 'mega-trial' involving 20,000 patients with inflammatory bowel disease! Characterization of the ideal patient population for 5-ASA – in terms of medical/surgical induction of remission, immediate/delayed initiation of therapy and disease location – remains to be clarified.

The utility of conventional corticosteroids in maintaining remission in Crohn's disease remains controversial. The European Cooperative Crohn's Disease Study noted that participants who entered remission on corticosteroids appeared to benefit from maintenance therapy (25). This effect was not as apparent in the National Cooperative Crohn's Disease Study (NCDDS) (26) or other trials (27). Brignola and co-workers (28) demonstrated that methylprednisolone 0.25 mg/kg/day versus placebo altered the relapse rate over the next six months in a group of patients perceived to be at high risk of relapse (11% versus 89%; difference 78%). Use of the new corticosteroid, budesonide, for maintenance therapy is under assessment. Based on the current literature, any benefit might be marginal (29-31).

A recent meta-analysis of trials of azathioprine in maintaining remission in 319 patients with Crohn's disease suggested that the chance of remaining in remission was doubled for patients receiving azathioprine therapy (odds ratio 2.27; 95% CI 1.76 to 2.93) (32). The largest trial of azathioprine therapy (NCDDS) failed to demonstrate efficacy regarding maintenance of remission (26).

Cyclosporine in maintenance of remission has been assessed in two trials. The largest, the Canadian Crohn's Relapse Prevention Trial, failed to demonstrate any efficacy in maintenance of remission (33). In fact, more patients on cyclosporine than on placebo relapsed (33). The European Study Group also failed to demonstrate any effect on sustained remission in a one-year, placebo controlled trial of a similar dose (5 mg/kg/day) of cyclosporine (34).

Recently a placebo controlled trial of metronidazole

20 mg/kg/day for 12 weeks demonstrated a significant reduction in severe endoscopic recurrence ($i_{3-4}$) (35) at 12 weeks. The number of clinical recurrences at 12 months was also reduced (25% versus 7%; difference 18%; 95% CI –1% to 37%) (36). In a small pilot study more clarithromycin-treated patients remained in sustained remission versus those receiving placebo (37). Further studies with antibiotics are warranted.

Nutritional therapy, particularly use of elimination diets for patients who have entered remission, has its advocates (38). A recent study involving more than 136 patients demonstrated modest benefit for those who entered remission on an elemental diet followed by an elimination diet (62% relapse rate at 24 months), compared with those randomized to corticosteroids and regular diet (79% relapse rate at 24 months) (39).

The Bologna group has recently assessed a new delivery formulation for eicosapentaenic acid (40). The new formulation consists of an enteric-coated capsule that releases beyond the stomach and should increase the palatability of the preparation. In a group of patients with Crohn's disease in remission considered to be at high risk for recurrence, only 32% of patients who received eicosapentaenic acid relapsed versus 73% of those randomized to placebo.

## CONCLUSIONS

What really works? 5-ASA-containing drugs are effective in maintaining remission in patients with ulcerative colitis. The usefulness of 5-ASA-containing drugs in patients with Crohn's disease is not as impressive, and their utility should be considered on a case by case basis. 5-ASA-containing drugs should be considered as part of a maintenance regimen, particularly in patients with frequent recurrences. Immunosuppressants appear to be beneficial in maintaining remission in Crohn's disease and should be considered in chronic relapsers.

## REFERENCES


1. Edwards F, Truelove SC. The course and prognosis of ulcerative colitis I. Short-term prognosis. Gut 1963;4:299-308.
2. Edwards F, Truelove SC. The course and prognosis of ulcerative colitis II. Long-term prognosis. Gut 1963;4:309-15.
3. Kornbluth AA, Salomon P, Sacks HS, Mitty R, Janowitz HD. Meta-analysis of the effectiveness of current drug therapy of ulcerative colitis. J Clin Gastroenterol 1993;16:215-8.
4. Azad Khan AK, Piris J, Truelove SC, Howes DT. An optimum dose of sulphasalazine for maintenance treatment in ulcerative colitis. Gut 1980;21:232-40.
5. Miner P, Schwartz J, Aora S, et al. Maintenance of remission in ulcerative colitis (UC) patients with controlled-release mesalamine capsules (Pentasa). Gastroenterology 1992;102:A666. (Abst)
6. Hanauer S, Powers B, Robinson M, et al. Maintenance of remission of ulcerative colitis by mesalamine (Asacol) vs placebo. Gastroenterology 1994;106:A696. (Abst)
7. Wright JP, O'Keefe EA, Cuming L, Jaskiewicz K. Olsalazine in maintenance of clinical remission in patients with ulcerative colitis. Dig Dis Sci 1993;38:1837-42.
8. Sutherland LR, May GR, Shaffer EA. Sulfasalazine revisited: A meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. Ann Intern Med 1993;118:540-9.
9. Kjærgaard N, Ambrosius Christensen L, Lauritsen JG, Norby Rasmussen S, Honoré Hansen S. Effects of mesalazine substitution on salicylazo-sulfapyridine-induced seminal abnormalities in men with ulcerative colitis. Scand J Gastroenterol 1989;24:891-6.
10. Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. BMJ 1959;i:387-94.
11. Lennard-Jones JE, Misiewicz JJ, Connell AM, Baron JH, Jones FA. Prednisone as maintenance treatment for ulcerative colitis in remission. Lancet 1965;i:188-9.
12. Powell-Tuck J, Parkins RA. A controlled trial of alternate day prednisolone as a maintenance treatment for ulcerative colitis in remission. Digestion 1981;22:263-70.
13. Hawthorne AB, Logan RFA, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. BMJ 1992;305:20-2.
14. Gilat T, Leichtman G, Delpre G, Eshchar J, Bar Meir S, Fireman Z. A comparison of metronidazole and sulfasalazine in the maintenance of patients with ulcerative colitis. J Clin Gastroenterol 1989;11:392-5.
15. Lobo AJ, Burke dA, Sobala GM, Axon ATR. Oral tobramycin in ulcerative colitis: Effect on maintenance of remission. Aliment Pharmacol Ther 1993;7:155-8.
16. Sutherland LR. 5-aminosalicylates for prevention of recurrence in patients with Crohn's disease: Time for a reappraisal? J Clin Gastroenterol 1991;13:5-7. (Edit)
17. Ewe K, Herfarth C, Malchow H, Jesdinsky HJ. Postoperative recurrence of Crohn's disease in relation to radicality of operation and sulfasalazine prophylaxis: A multicentre trial. Digestion 1989;42:224-32.
18. Brignola C, Cottone M, Pera A, et al. Mesalamine in the prevention of endoscopic recurrence after intestinal resection in Crohn's disease. Gastroenterology 1995;108:345-9.
19. McLeod RS, Wolff BG, Steinhart AH, et al. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. Gastroenterology 1995;109:404-13.
20. Thomson ABR, Wright JP, Vatn M, et al. Mesalazine (Mesasal/Claversal) 1.5 g bid daily versus placebo in the maintenance of remission of patients with Crohn's disease. Aliment Pharmacol Ther 1995;9:673-84.
21. Sutherland LR, Martin F, Bailey RJ, et al. 5-aminosalicylic acid (Pentasa) in the maintenance of remission of Crohn's disease. Gastroenterology 1995;108:A924. (Abst)
22. Modigliani R, Colombel JF, Dupas JL, et al. Mesalamine in Crohn's disease with steroid-induced remission: Effect on steroid withdrawal and remission maintenance. Gastroenterology 1996;100:688-93.
23. Messori A, Brignola C, Trallori G, et al. Effectiveness of 5-aminosalicylic acid for maintaining remission in patients with Crohn's disease: A meta-analysis. Am J Gastroenterol 1994;89:692-8.
24. Steinhart AH, Hemphill DJ, Greenberg GR. Sulfasalazine and mesalazine for the maintenance therapy of Crohn's disease: A meta-analysis. Am J Gastroenterol 1994;89:2116-24.
25. Malchow H, Ewe K, Brandes JW, et al. European Cooperative Crohn's Disease Study (ECCDS): Results of drug treatment. Gastroenterology 1984;86:249-66.
26. Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: Results of drug treatment. Gastroenterology 1979;77:847-69.
27. Smith RC, Rhodes J, Heatley RV, et al. Low dose steroids and clinical relapse in Crohn's disease: a controlled trial. Gut 1978;19:606-10.
28. Brignola C, Campieri M, Farruggia P, et al. The possible utility of steroids in the prevention of relapses of Crohn's disease in remission. A preliminary study. J Clin Gastroenterol 1988;10:631-4.
29. Lofberg R, Rutgeerts P, Malchow H, et al. Budesonide CIR for maintenance of remission in ileocecal Crohn's disease. A European multicenter placebo controlled trial for 12 months. Gastroenterology 1994;106:A722. (Abst)
30. Greenberg GR, Feagan BG, Martin F, et al. Oral budesonide as maintenance treatment for Crohn's disease. Gastroenterology 1995;108:A827.
31. Gross V, Andus T, Ecker KW, et al. Oral pH-modified release budesonide for maintenance of steroid induced remission in Crohn's disease – An interim analysis. Gastroenterology 1995;108:A828.
32. Pearson DC, May GR, Fick GH, Sutherland LR. Azathiprine and 6-mercaptopurine in Crohn's disease. A meta-analysis. Ann Intern Med 1995;122:132-42.

33. Feagan BG, Donald JWD, Rochon J, et al. Low-dose cyclosporine for the treatment of Crohn's disease. N Engl J Med 1994;330:1846-51.
34. Stange EF, Modigliani R, Peña AS, et al. European trial of cyclosporine in chronic active Crohn's disease: A 12-month study. Gastroenterology 1995;109:774-82.
35. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956-63.
36. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995;108:1617-21.
37. Graham DY, Al-Assi MT, Robinson M. Prolonged remission in Crohn's disease following therapy for *Mycobacterium paratuberculosis* infection. Gastroenterology 1995;108:A926. (Abst)
38. Jones VA. Crohn's disease: Maintenance of remission by diet. Lancet 1985;ii:177-80.
39. Riordan AM, Hunter JO, Cowan RE, et al. Treatment of active Crohn's disease by exclusion diet: East Anglian multicentre controlled trial. Lancet 1993;342:1131-4.
40. Belluzzi A, Brignola C, Campieri M, et al. New fish oil derivative for preventing clinical relapses in Crohn's disease: A double blind placebo controlled randomized trial. Gastroenterology 1995;108:A781. (Abst)