Maintenance therapy for inflammatory bowel disease: What really works

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Almost inherent in the definition of inflammatory bowel disease is its propensity for recurrent episodes or disease flares. 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

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).
demonstrated that mesalamine 3.0 g/day, given to patients who had failed previous therapy, was more effective than placebo in preventing relapse over the first two years (17).

Three additional studies were reported in 1995. McLeod and associates (19) compared sulfasalazine with placebo-treated patients. Three additional studies were reported in 1995. McLeod and associates (19) compared the effects of mesalamine on endoscopic recurrence for mesalamine-treated patients. 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 endoscopic recurrence 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 effective in the management of peritonitis, was not as apparent in the National Cooperative Crohn’s Disease Study (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 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 and disease location – remains to be clarified.

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_{max}) 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
