

THERAPY UPDATE

Which 5-ASA?

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When Asacol commands 65% of the UK market, can so many British gastroenterologists be wrong? Possibly. The market leader in France is Pentasa (72%) and is Salofalk in Germany (57%). In Canada it is Asacol (46%). Nevertheless, a Cochrane review of 11 trials involving 1598 patients showed that sulphasalazine was more effective than other 5-aminosalicylic acid (5-ASA) drugs for maintaining remission in ulcerative colitis (odds ratio (OR) 1.29, confidence interval (CI) 1.06–1.57).¹ Diagnosis, disease location, activity, side effect profile, efficacy, and cost all affect the choice of 5-ASA.

5-ASA acts on and is metabolised by intestinal epithelial cells. Consequently, ulcerative colitis (a mucosal disease) is more susceptible to treatment by 5-ASA than transmural Crohn's disease. Mega doses of mesalazine (≥ 4 g/day) may be an initial alternative to steroids for mild-moderately active ulcerative colitis and reduce the risk of relapse after small intestinal (but not colonic) resection for Crohn's disease.² If such high doses are to be used it makes sense to use a 5-ASA with little systemic absorption. Plasma 5-ASA concentrations are approximately 2 $\mu\text{mol/l}$ for sulphasalazine, Pentasa, olsalazine, or balsalazide, compared with >6 $\mu\text{mol/l}$ for Asacol and >13 $\mu\text{mol/l}$ for Salofalk.³

As far as disease location is concerned, the key to treatment is a high concentration of 5-ASA at the site of inflammation. Suppositories are often appropriate for proctitis because $>90\%$ liquid 5-ASA enemas bypass the rectum.⁴ For active proctitis, a 1 g Pentasa suppository is more rapidly effective than two 500 mg Claversal (similar to Asacol) suppositories⁵ and also maintains remission.⁶ For distal or left sided disease, suppositories can be combined with enemas. Asacol foam is better tolerated than liquid 5-ASA, while expensive Salofalk enemas provide double the necessary dose. The optimum dose for topical treatment is 1 g.⁷

The main role for 5-ASA remains maintenance of remission in ulcerative colitis. Individual 5-ASA derivatives all show comparable efficacy to sulphasalazine but the therapeutic advantage of the parent compound¹ should be noted. Azo bonded compounds may be better for distal disease, which predominates in ulcerative colitis, and olsalazine was better than Asacol⁸ in one of the very few direct comparisons between 5-ASA derivatives. The advantage of balsalazide over Asacol⁹ however, welcomed as an azo bonded compound with few side effects, has been disappointing. In any case, the theoretical advantage of azo bonded compounds for distal disease can be overcome simply by increasing the dose of mesalazine.

The principal advantage of 5-ASA derivatives over sulphasalazine is that they are better tolerated. In the Cochrane review of maintenance therapy¹ however, sulphasalazine and 5-ASA had similar adverse event profiles (OR 1.16 (CI 0.62–2.16), and 1.31 (CI 0.86–1.99), respectively). The numbers needed to harm also favoured sulphasalazine, being 171 and 78, respectively. Even so,

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Key points

- Diagnosis, disease location, activity, side effect profile, efficacy, and cost all affect the choice of 5-ASA.
- Sulphasalazine has a small but significant benefit over 5-ASA derivatives for maintaining remission in ulcerative colitis and may harm fewer patients.
- Mesalazine dose is more important than the delivery system.
- Pentasa suppositories are best for proctitis.
- Combine suppositories and enemas for distal disease.

some side effects can be used to therapeutic advantage. Olsalazine induced diarrhoea may help patients with distal disease and proximal constipation. Sulphasalazine may be better for patients with colitis associated arthropathy. Maintenance therapy with all 5-ASA drugs probably reduces the risk of colorectal cancer by 75% (OR 0.25, CI 0.13–0.48),¹⁰ which supports long term treatment in those with extensive colitis.

Cost is a final consideration and as a clinical director in the UK, sulphasalazine (tolerated by 80% at 2 g/day, costing the NHS £110 pa) still deserves serious consideration. The alternatives, all tolerated by about 90%, are 3–5-fold more expensive, which mounts up over the decades. An average primary care trust serving 170 000 people would save in the region of £10 000 pa if most patients with ulcerative colitis were prescribed the least expensive mesalazine. If general practitioners can be persuaded to contribute this saving to the salary of an inflammatory bowel disease nurse specialist, then so much the better!

And if I had one choice for a desert island? Pentasa wins on dose flexibility, different preparations, and low systemic absorption, but in practice I use all 5-ASA derivatives. The patient often declares a preference and that is the key to compliance.

Conflict of interest. Dr Travis has cheerfully enjoyed hospitality from all manufacturers of 5-ASA derivatives and has done advisory work for Ferring Pharmaceuticals, Pharmacia, and SmithKline Beecham.

REFERENCES

- 1 Sutherland LR, Roth D, Beck P, *et al.* Oral 5-aminosalicylic acid for maintaining remission in ulcerative colitis (Cochrane review). In: *The Cochrane Library*, vol 1. Oxford: Update Software, 2002.
- 2 Lochs H, Mayer M, Fleig WE, *et al.* Prophylaxis of post-operative relapse in Crohn's disease with mesalazine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* 2000;**118**:264–73.
- 3 Laursen LS, Stokholm M, Bukhave K, *et al.* Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values and urinary excretion. *Gut* 1990;**31**:1271–6.
- 4 Van Bodegraven AA, Boer RO, Lourens J, *et al.* Distribution of mesalazine enemas in active and quiescent ulcerative colitis. *Aliment Pharmacol Ther* 1996;**10**:327–32.

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- 5 **Gionchetti P**, Rissolo F, Ventura A, *et al*. Comparison of mesalazine suppositories in proctitis and distal proctosigmoiditis. *Aliment Pharmacol Ther* 1997;**11**:1053–7.
- 6 **Marteau P**, Crand J, Foucault M, *et al*. Use of mesalazine slow-release suppositories 1g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. *Gut* 1998;**42**:195–9.
- 7 **Hanauer SB**. Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: results of a multicentered placebo-controlled trial. The U.S. PENTASA Enema Study Group. *Inflamm Bowel Dis* 1998;**4**:79–83.
- 8 **Courtney M**, Nunes D, Bergin C, *et al*. Randomised comparison of olsalazine and mesalazine in prevention of relapses in ulcerative colitis. *Lancet* 1992;**339**:1279–81.
- 9 **Green JR**, Gibson JA, Kerr GD, *et al*. Maintenance of remission of ulcerative colitis: a comparison between balsalazide 3 g daily and mesalazine 1.2 g daily over 12 months. ABACUS Investigator group. *Aliment Pharmacol Ther* 1998;**12**:1207–16.
- 10 **Eaden J**, Abrams K, Ekbohm A, *et al*. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther* 2000;**14**:145–53.