Mesalazine: is changing to the cheapest really cost-effective?

With over a dozen mesalazine products available for ulcerative colitis, choosing between them can be difficult. Anja St.Clair Jones discusses some of the factors that prescribers should consider. Choice should not be based on cost alone, she says, but should take into account current management strategies and adherence issues.

Mesalazine is well established as the mainstay of treatment to manage mild to moderate ulcerative colitis (see “Ulcerative colitis: background information” Panel p2). Most clinicians are familiar with its use but may feel unsure about the different products, their efficacy and their place in therapy. The aim of treatment is:

- Symptom relief
- Induction and maintenance of remission
- Mucosal healing
- Avoiding surgery
- Reducing the likelihood of cancer

A number of reviews have considered the impact of different mesalazine products and a recent one of modified release formulations advocated the substitution of generic versions as a pragmatic, cost-saving approach for the NHS. This review, which excluded some preparations owing to their different release mechanisms, suggested that Mesren 400mg tablets be prescribed instead of the market leader Asacol MR for all new patients and those who require a change to their drug regimen. I believe, however, that this proposed approach might only result in short-term savings. Once current strategies in management of ulcerative colitis and adherence issues are taken into account it is possible that change to the cheaper preparation could result in decreased maintenance of remission, more hospital admissions and, perhaps, an increased incidence of colorectal cancer.

Recent trials have looked at high-dose or once-daily treatment regimens, or both. The non-inferiority of once-daily regimens together with mounting evidence of the negative impact of non-adherence is changing the way management of ulcerative colitis is approached.

There is also a trend in practice towards the use of higher doses. According to the British Society of Gastroenterology, 4g/day of mesalazine is more effective than placebo for inducing remission in mild to moderate ulcerative colitis, and greater clinical improvement (but not necessarily remission) is associated with doses greater than 3g/day. The Ascend II trial, comparing 1,600mg tds with 800mg of Asacol tds for six weeks, indicated that patients with moderate ulcerative colitis did better on the higher dose, with a 72 per cent response compared with 59 per cent (P=0.036).

Currently, however, for many preparations, the British National Formulary lists the dose for acute attacks as 2.4g/day. And for most preparations, it says that doses for both acute attacks and remission should be divided.

The European Crohn’s and Colitis Organisation (ECCO) recommends a minimum daily dose of 1g to maintain remission but evidence is emerging that daily doses of 2g and above may be more effective.

Non-adherence

Non-adherence is generally regarded as taking less than 80 per cent of prescribed medicine. Adherence is a particular issue in patients in remission (in an acute attack patients are more likely to comply with treatment). For example, Kane et al found that overall adherence was around 40 per cent in patients using mesalazine for maintenance of quiescent ulcerative colitis. Similar results were shown in the Manitoba inflammatory bowel diseases cohort study, in which about a third of patients were found to be low adherers.

The clinical impact of non-adherence is considerable. It increases the chance of relapse to 61 per cent in non-adherers compared with 11 per cent in adherers (P<0.001), reduces quality of life, and increases colorectal cancer risk to 31 per cent in non-adherers in comparison with 3 per cent in adherers (P=0.001).

A review by Hawthorne confirms that adherence to mesalazine therapy reduces the risk of colorectal cancer by 75 per cent and favours a multidisciplinary team approach to improve adherence rates.

In 2004, the economic cost for caring for patients with inflammatory bowel diseases over six months in the UK ranged from £73 to £33,254, with the mean cost for ulcerative colitis patients being £1,256. Only 14 per cent of patients in the study needed admission to hospital but they accounted for 49 per cent of total secondary care cost.

Strategies to achieve adherence

In a systematic review Kane also found varied factors and reasons for non-adherence, including disease duration, male gender, single status, full-time employment and three times a day dosing. Patients gave forgetfulness, questioning the need for medication, inconvenient regimens and having to take many tablets as reasons for non-adherence.

In 2009, the National Institute for Health and Clinical Excellence clinical guideline CG76, “Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence”, recommended simplifying drug regimens in order to tailor therapies to the needs of individual patients, integrating regimens into their lives. Addressing barriers to adherence resulting from patients’ beliefs is complex and proposed interventions are probably of limited benefit, but offering simpler, less intrusive drug delivery methods are of proven value.

Patients tend to prefer once daily oral formulations. With the trend of treatment to higher dose regimen tablet burden needs to be reduced to improve compliance. Higher dose preparations, such as Asacol 800mg tablets and Pentasa 2g sachets, have been formulated for the treatment of active disease.

Rectal preparations

ECCO guidelines advise adding topical (rectal) mesalazine to oral because oral mesalazine alone is less effective in improving symptoms. However, rectal preparations tend to be less acceptable than oral preparations and are associated with leakage, retention issues and bloating, and can reduce adherence to therapy. Therefore they tend to be used in the treatment of active distal disease or in combination with oral formulations for extensive disease. A review of rectal preparations is outside the scope of this article but it should be noted that, as with oral preparations, different rectal formulations deliver mesalazine to different parts of the distal colon, in different concentrations and with variable acceptability to patients.

Further considerations

Because the action of mesalazine is predominantly topical, the aim is to deliver active drug to the site of inflammation, with minimal systemic absorption. Only 15 per cent of patients initially presenting with...
**ULCERATIVE COLITIS: BACKGROUND INFORMATION**

Ulcerative colitis is a life-long disease arising from interaction between genetic and environmental factors observed predominantly in developed countries. The condition is characterised by diffuse mucosal inflammation which can be divided into distal (proctitis and proctosigmoiditis) or more extensive disease (left sided colitis, extensive colitis and pancolitis). The Montreal classification is favoured by the European Crohn’s and Colitis Organisation (ECCO) to describe the disease extent, as follows:

- **Proctitis (E1)** Limited to the rectum (ie, extent of inflammation is distal to the rectosigmoid junction)
- **Left-sided (E2)** Limited to the proportion of the colon distal to the splenic flexure (analogous to “distal” colitis)
- **Extensive (E3)** Extends proximal to the splenic flexure (includes pancolitis)

**About the disease**

In the UK, about one in 1,000 people develop ulcerative colitis, most commonly between the ages of 10 and 40 years.

**Symptoms and diagnosis**

Symptoms include:

- Mild to severe diarrhoea (which can be watery and contain mucus or blood) or urgency to get to the toilet but with nothing to pass
- Cramps in the abdomen
- Pain on passing stools
- Feeling generally unwell (especially if an attack affects a large portion of the large intestine or is prolonged)

Diagnosis usually involves a sigmoidoscopy or colonoscopy to look at the appearance of the lining of the rectum and colon. The mucosa appears inflamed and ulcered.

**Disease activity**

Management is dictated not only by disease distribution but by disease activity, which ECCO has classified into four groups: remission, mild, moderate and severe. However, ECCO did not agree criteria to assess these and the Trueove and Witts classification still seems to be a favoured approach. This classes the disease as mild, moderate or severe using the following factors:

- Number of bloody stools per day (<4 mild; 4–6 moderate; ≥7 severe)
- Pulse (>90bp mild; >90bp moderate; >90bp severe)
- Temperature (>37.5C mild; >37.8C moderate; >37.8C severe)
- Haemoglobin (>11.5g/dL mild; >10.5g/dL moderate; <10.5g/dL severe)
- Erythrocyte sedimentation rate (>20mm/h mild, >30mm/h moderate, >30mm/h severe) or C-reactive protein (>3mg/L mild, >30mg/L moderate, >30mg/L severe)

It should be noted that a review in 2007 of activity indices (and clinical trial endpoints) concluded that “an optimal scoring instrument for ulcerative colitis is still to be developed and will require validation before extensive use in clinical trials can be promoted.”

Ulcerative colitis is a relapsing condition, with acute attacks and periods of remission. More than 50 per cent of patients with a flare up have a relapse within a year. The relapse rate for patients in remission and not taking any medicine is 38–76 per cent.

**Treatment options**

Treatment goals are to control symptoms and maintain remission. Drugs used include aminosalicylates, immunosuppressants, steroids and laxatives (proctitis sufferers resist the urge of a bowel movement because it is painful and constipation results) but, with so many types of ulcerative colitis described (eg, mild, active, quiescent, left-sided) choice can be confused. Rectal preparations are usually used during attacks and for proctitis (acute and remission). More detailed recommendations for different types of ulcerative colitis from ECCO are available at www.ecco-ibd.eu. In general, however, for mild to moderate disease, mesalazine is prescribed initially. If two episodes of steroids are needed within a year, therapy will be stepped up to thiopurines, before an anti-tumour necrosis factor drug.

Steroids are only used to induce remission. In the UK, a recommended steroid regimen is prednisolone 40mg daily for one week, 30mg daily for one week, then 20mg daily for two weeks followed by a review and further step down, depending on response, until the prednisolone is stopped. A severe attack can be life-threatening and must be referred to a hospital for intravenous steroid therapy. About a quarter of people with ulcerative colitis will need surgery.

**First-line therapy**

The original treatment was sulfasalazine but side effects, including exfoliating dermatitis, are common. Choice of aminosalicylate is influenced by tolerability and induction and maintenance of remission in mild to moderate disease. It is safe in long-term use. The drug has a topical action on epithelial cells and is, therefore, more active in ulcerative colitis (a mucosal disease) than in Crohn’s disease (a transmural disease). Oral mesalazine is completely absorbed in the small intestine but poorly absorbed in the colon.

To obtain a high concentration of the drug at the site of inflammation it is essential to minimise systemic exposure and ensure topical delivery to the affected tissue. As for choice of mesalazine, this cannot be made on grounds of efficacy alone — route, pattern, dose frequency, patient acceptability, cost and availability are also relevant factors (see main article).

**Prognosis and lifestyle**

In most cases ulcerative colitis starts in the rectum (proctitis). In some patients the disease spreads up to affect some, or all, of the colon. People who have had ulcerative colitis for a number of years are at a higher risk of developing colorectal cancer, especially those who have frequent flare-ups affecting the whole of the large intestine.

People with ulcerative colitis do not usually need any special diet but a high-fibre diet may help those with proctitis to avoid constipation. Iron tablets will be needed in those who develop anaemia (due to blood lost in stools). Patients taking steroids, especially those needing more than two courses per year, should take calcium and vitamin D.

**Resources**

- Standards for NHS services for inflammatory bowel disease are available at www.ibdstandards.org.uk.

**Signposting**

- Information and support for people with ulcerative colitis is available from Crohn’s and Colitis UK (www.nacc.org.uk).
Panel 1: Formulation and Release Characteristics of Oral Mesalazine MR *

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Optimal drug release pH</th>
<th>Site of drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asacol MR</td>
<td>400mg: Enteric coated with Eudragit S; 800mg: Enteric coated with layer of Eudragit S followed by Eudragit S-L</td>
<td>pH dependent delayed release (&gt;7)</td>
<td>Terminal ileum and large bowel (colon and rectum)</td>
</tr>
<tr>
<td>Ipocol</td>
<td>Enteric coated with Eudragit S</td>
<td>&gt;7</td>
<td>Terminal ileum and colon</td>
</tr>
<tr>
<td>Mesren MR</td>
<td>Enteric coated with Eudragit S</td>
<td>&gt;7</td>
<td>Terminal ileum and colon</td>
</tr>
<tr>
<td>Mezavant XL</td>
<td>Film coated with methacrylate copolymers type A, type B</td>
<td>Gastroresistant coating with lipophilic and hydrophilic matrix(7)</td>
<td>Colon</td>
</tr>
<tr>
<td>Pentasa</td>
<td>Ethylcellulose coated microgranules</td>
<td>Diffusion through semi-permeable membrane (enteral pH)</td>
<td>Duodenum to rectum</td>
</tr>
<tr>
<td>Salofalk</td>
<td>Tablets: Enteric coated with Eudragit L; Granules: Eudragit L plus matrix granule structure</td>
<td>pH dependent delayed release (&gt;6) (granules have extra delayed release)</td>
<td>Terminal ileum and colon</td>
</tr>
</tbody>
</table>

*Adapted from UK Medicines Information Q&A 67.2. What are the differences between different brands of mesalazine tablets?

Panel 2: Recent Mesalazine Trials of Maintenance of Remission in Mild to Moderate Ulcerative Colitis

Sandborne et al 2009 16 Once a day dosing of Asacol 400mg tablets was compared with twice a day dosing to achieve doses between 1.6g and 2.4g/day for 12 months (n=1,023). Using the simple clinical colitis activity index (SCCAI), maintenance of remission was 85 per cent in both groups. In other words, non-inferiority was found. The study was not powered to prove superiority and 70 per cent of patients were already taking 2.4g/d at the start of the trial.

Dignass et al 2009 17 A dose of 1g twice a day of pentasa granules was compared with 2g daily in 392 patients for 12 months. The ulcerative colitis disease activity index (UCDAI) was used for assessment. At one year, it was found that maintenance of remission in the twice-a-day group was 59 per cent compared with 71 per cent in the once-daily group (P=0.024). However, the trial population was small.

Kruise et al 2008 18 Three regimens of Salofalk granules were compared: 3.0g daily, 1.5g daily and 0.5g three times a day, for 12 months (n=647). At one year, maintenance of remission was 75 per cent, 61 per cent and 69 per cent, respectively, suggesting that 3g daily is the more efficacious dosage. However, this research is accessible in abstract form only so in depth analysis of data is not possible. Assessment indices used were clinical activity index (CAI) and endoscopy index (EI).

Kamm et al 2009 19 A regimen of Mezavant tablets 2.4g daily was compared with 1.2g twice a day for 12 months (n=459). Maintenance of remission in the once-daily regimen was 64 per cent compared with 68 per cent in the twice-daily regimen (P=0.351). The UCDAI was used for assessment.

Recent evidence

Despite individual trial results, systematic reviews fail to find conclusive dose-dependent responses to mesalazine therapies, partly due to study designs and partly due to the fact that attainment of remission is affected by disease severity, duration and interpatient variability. This might reflect the inability of current formulations to deliver consistently therapeutic drug levels to affected tissue — gut function, distribution of gut content and effect of the drug on gut flora is still poorly understood and these factors may all affect efficacy.

A Cochrane review in 2009 concluded that the differences in efficacy are likely to be marginal and further trials should look at enhancing patient adherence with medication rather than comparing the efficacy of various mesalazine agents. 15

Recent studies on maintenance of remission in quiescent disease are outlined in Panel 2. Remission rates between studies cannot be compared due to difficulties in interpretation and differences of study design. Furthermore, unlike Crohn’s disease, the lack of mild to moderate relapse of ulcerative colitis found both preparations to be equally effective. 1 Mesren has not been clinically compared with other preparations (it is not a requirement for licensing because the product has the same bioequivalence as Asacol MR). It is also worth noting that Asacol formulations in different countries are not equivalent due to different manufacturing processes and coating so, for example, US trial data might not be valid for comparison with UK data.

Prescribing & medicines management

Anja St.Clair Jones will be available to answer questions online on the topic of this article until 8 September 2010

Ask the expert www.pjonline.com
of standard indices for ulcerative colitis (see “Ulcerative colitis” Panel) precludes the collection of consistent treatment efficacy data. It should be noted that most of the assessment indices used in these recent studies are unvalidated (with the exception of clinical activity index, which was validated in one study) or not formally validated (ulcerated colitis activity index). Moreover, because assessment indices are inconsistent, as was the selection of patient groups and subgroups, comparisons across these studies are difficult.

Recent research is mainly concerned with increased dose range and formulations that reduce the pill burden on patients. Adherence is increasingly included as secondary endpoints in the maintenance of quiescent ulcerative colitis studies underlining the increasing importance of this factor on maintenance of remission.

The need to develop standard assessment indices for ulcerative colitis is paramount to evaluate the efficacy of different formulations because only trial data can accurately determine the effect of formulation on response. Intraluminal concentration assessment methods remain limited in their usefulness.

**Costs**

Panel 3 compares pill burden, dosage and cost of recommended regimens. Asacol 800mg tablets are large and may not be acceptable to all patients. Pentasa may be a preferable option for maintenance of remission in view of cost and adherence issues discussed — one 2g sachet once daily compares favourably to Mesren and Asacol MR, in terms of reduced unit load burden. Salofalk has limited data but those reported so far seem to favour higher doses of 3g.

Currently, it is a patient-centred approach to management that will result in long-term cost-effectiveness.

**Conclusion**

Adherence to mesalazine treatment in is complex and multifactorial, and differs with time. Studies of several formulations of once daily dosing in induction and maintenance therapy have shown that once-daily dosing is efficacious and safe, that formulations are probably not of significant importance to the effect of mesalazine but that high strength and once-daily dosing may improve adherence.

Research has shown that divergence of adherence at month three (when maintenance treatment begins) affects the maintenance of remission so it is imperative to reduce pill burden. It is questionable if generic low-dose tablets offer a patient-centred reliable alternative — like Asacol MR, they are not licensed to be used once a day.

It remains to be investigated if a change to once-daily dosing and low tablet loads reduces hospital admissions and long-term incidence of colorectal cancer. Ancedtal reports exist but this must be a priority area of research in the future.

---

**DECLARATION OF INTEREST** The author has provided training support work to Ferring in the past.

**References**


This article has not been peer-reviewed.

---

**The author**

Antja St.Clair Jones, MRPharmS, is lead pharmacist, surgery and digestive diseases, at Brighton and Sussex University Hospitals NHS Trust.