Leading article

Medical treatment of ulcerative colitis: scoring the advances

There is no doubt that the outlook for the patient with ulcerative colitis is better than it was 50 years ago when sulphasalazine was first introduced.1 Much of the decreased mortality can be attributed to corticosteroids first shown to be effective in ulcerative colitis in 1952. The next milestone was widespread prescription of sulphasalazine, once it had been clearly established that it prolongs remission.2 In the following 25 years much has happened, but have there been major therapeutic advances?

Oral treatments

SALICYLATES

The demonstration that 5 amino salicylic acid (mesalazine) could induce remission in more patients with active disease than sulphapyridine3 is rightly regarded as seminal and has been supported by subsequent evidence of activity for maintenance of remission.6–12 It is worth remembering that these studies did not prove that unsplit sulphasalazine had no intrinsic activity (nor, incidentally, that sulphapyridine was devoid of therapeutic activity, though the latter seems likely).

The major advance which such data imply has not yet occurred. If sulphasalazine acts solely through 5 amino salicylic acid it should be possible to develop drugs capable of delivering much greater amounts to the colon without sulphapyridine related side effects. Alternatives to sulphasalazine in which sulphapyridine has been eliminated have, of course, been developed. Those at the most advanced stage illustrate the two main approaches that have been adopted. Polymer coated mesalazine (marketed as Asacol in the United Kingdom) uses the principle of delaying release, in order to avoid small intestinal absorption until the drug reaches the colon, and this has been shown to occur.13–15 Published data are too limited to be sure that premature dissolution in the small intestine does not happen in some patients – for example, in those with slow transit, or high small intestinal pH. This is important not only because it would limit therapeutic efficacy, but also because mesalazine is potentially nephrotoxic.16

Table

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<tr>
<th>Chemical name</th>
<th>Generic name</th>
<th>Trade name(s)</th>
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<tbody>
<tr>
<td>5 aminosalicylic acid (5ASA)</td>
<td>Mesalazine</td>
<td>Asacol, Claversal, Pentasa, Salofalk</td>
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<td>Azidosalicylate (ADS)</td>
<td>Olsalazine</td>
<td>Dipentum</td>
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<td>Carboxyethyl-carbamoylphenol azosalicylate</td>
<td>Balsalazide</td>
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<td>4 aminosalicylic acid (4ASA)</td>
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<td>para aminosalicylic acid (PAS)</td>
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serum concentrations of 5 amino salicylic acid after single doses of polymer coated mesalazine have been higher than after sulphasalazine, although accumulation does not seem to occur with more prolonged dosing.

The second approach, that of using an alternative carrier to sulphapyridine, is illustrated by azodisalicylate (olsalazine, Dipentum), where two molecules of mesalazine have been joined together by a diazo bond, so that they each act as a carrier for the other. This drug too achieves high concentrations of free mesalazine in the faeces but here a different problem has arisen. About 6% of patients experience drug induced diarrhoea caused by a secretory action of unsplit olsalazine in the small intestine.

Are higher doses more effective?
The new salicylates are thus effective agents for the treatment of relapse and maintenance of remission. Some trials have used doses which probably deliver more mesalazine to the colon than comparative doses of sulphapyridine, but here it is unclear whether greater therapeutic potency results. In one maintenance study 22% of patients relapsed over six months when taking 2.7 g of mesalazine as Asacol, compared with 20% of those taking 0.9 g of mesalazine in sulphasalazine. This was a disappointing result, as earlier studies had shown that the response to sulphasalazine was dose dependent. In another study of treatment of relapse Asacol, giving daily doses of mesalazine 0.8 g and 2.4 g, and sulphasalazine giving daily doses of 0.84 g, were compared. Significantly more patients taking high dose Asacol had sigmoidoscopic improvement, compared with sulphasalazine. In this study there were no significant dose dependent differences for mesalazine and there were trends suggesting that patients on low dose Asacol were doing better than those taking sulphasalazine. Similarly a recent report found patients taking olsalazine 2 g/day (2 g mesalazine) for relapse had less bleeding than those taking sulphasalazine 3 g/day (1.1 g mesalazine), although sulphasalazine performed better if other variables such as the number of unformed stools were considered.

The answers to two interesting questions thus remain unclear. Pharmacologically it remains possible that sulphapyridine possesses intrinsic activity, in addition to that residing in mesalazine. Clinically it is not clear how high the dose can be safely pushed with these two agents and whether better treatment would then result. Conceivably there is more scope for such megadose therapy with one of the other agents such as balsalazide, in which mesalazine is linked to the poorly absorbed carrier, 4 aminobenzoyl-6-alanine. This drug has clinical efficacy similar to sulphapyridine when given at similar dosage, but with significantly fewer side effects. On one measure (change in haemoglobin) there were suggestions that it might be superior, but such observations need confirmation. On the limited data so far available, balsalazide has a therapeutic index which might allow delivery of much higher doses of mesalazine with an acceptable incidence of side effects.

Even if these alternatives to sulphapyridine have not been major therapeutic advances for most patients with ulcerative colitis, they have been a welcome addition for the large minority who are unable to tolerate sulphapyridine. In such patients polymer coated mesalazine and olsalazine are effective acute and maintenance treatments, although the rate of withdrawals because of intolerance (between 13 and 15%) is higher than in
unselected patients. The newer salicylates are also an advance in the sense that they lack sulphasalazine's ability to cause sulphapyridine mediated infertility.

CORTICOSTEROIDS
These remain the main acute treatment, but their use is limited by side effects which make them unsuitable for maintenance. Orally active corticosteroids with purely topical activity, or with first pass metabolism so effective that no drug reaches the systemic circulation would be a major advance for two reasons. First, substantial increases in dose which this would allow might improve the effectiveness of corticosteroids in the treatment of relapse. Second, it would also be possible to re-explore a role for these drugs in the maintenance of remission. Results with the poorly absorbed preparations, beclomethasone, budesonide and tixocortol pivolate have shown that such drugs are undoubtedly active topical agents for distal disease. This is an encouraging, but so far limited application.

AZATHIOPRINE
Despite inconsistencies in the data, many gastroenterologists accept that azathioprine has therapeutic value in Crohn's disease, acting as a 'steroid sparing agent', though this only means that steroid sparing was used as an end point in trials to show therapeutic efficacy; it would be almost equally logical to describe corticosteroids as azathioprine-sparing agents.

The position is much less clear in ulcerative colitis. In the largest trial of azathioprine, 80 patients in relapse were randomised to supplemental azathioprine, or placebo and followed for 12 months. By this time 16 patients on azathioprine and nine patients on placebo had no further relapses: no significant difference. Nevertheless, we are among those who perceive azathioprine, or 6 mercaptopurine as useful for patients with poorly controlled ulcerative colitis. The design of most trials has not been ideal for showing benefit. Although the mode of action of azathioprine is not clear, most of its immunological effects occur with considerable latency, so that maximum benefit cannot be expected for at least a month. A controlled trial of azathioprine withdrawal from patients in established remission on the drug is needed. If azathioprine proved effective in patients with chronic continuous disease who were dependent on corticosteroids, this would be an important advance, as such patients often progress to colectomy.

Topical treatments
SALICYLATES
Topical mesalazine is an effective treatment for proctosigmoiditis. In mild and moderate disease, Campieri and colleagues showed that a 4 g dose was more effective than hydrocortisone enemas, with clinical and sigmoidoscopic improvement in 93% of patients. Likewise, the Danish 5ASA group showed that lower doses were at least as effective as prednisolone enemas. Initial problems with stability in solution have now been overcome. 4 Aminosalicylic acid (which is but para aminosalicylic acid, renamed for intrarectal use by gastroenterologists) may be preferable as a cheaper and more stable preparation and is probably equally effective, though the choice of an optimal agent has not been fully resolved.
Topical treatment with high dose (4 g) mesalazine also works well in distal colitis refractory to conventional treatment. In the latter study treatment for two months resulted in a 25% rate of local side effects with irritation, anal fissures and one abscess, though this has not been a problem in other trials.

How topical salicylates work and whether the mechanism is the same as when salicylates are used orally, producing lower local concentrations, is not known. Perhaps their ability to irritate, by a predominantly physical mechanism is important, because mild irritants, sodium salicylate and sulphasalazine itself have all been shown to be (cyto)protective to other parts of the gut.

Although topical salicylates are not widely used they are an important advance for a subgroup of patients with poorly responsive chronic proctitis.

**TOPICAL STEROIDS – COSMETIC ADVANTAGES OF FOAMS**

There is now little doubt that steroid foams are effective and they are widely used. They appear to be as effective as enemas, but the comparative trials have been relatively small. They are much preferred by patients, largely on the grounds of convenience and acceptability. This suggests that development of a foam preparation of one of the salicylates for topical use would lead to more widespread adoption of these agents, which can be therapeutically superior to topical corticosteroids.

**Synopsis**

Recently, oenological prejudices were challenged by the use of a points scoring system (from 50 to 100) to evaluate wine in a book now widely regarded as one of the most authoritative. On this scale, a 1981 Chateau Citran described as ‘emaciated’ scored 65, a 1983 Chateau Kirwan scored 85, and a 1982 Petrus 100. If the same approach were used for drugs used in ulcerative colitis to quantify an advance over conditions existing at the time of its introduction how would they score? Because they were the first available drugs in their class and clearly constituted major advances, corticosteroids and sulphasalazine both score 95, the score being limited by a high level of side effects. The new salicylates score 75, because they extend the benefits of sulphasalazine to a minority of patients but they have the potential to score 90 if increased dosing and greater effectiveness over sulphasalazine can be achieved. Salicylate enemas score 80, because they advance treatment over topical corticosteroids for patients with resistant distal disease, but the mode of delivery needs improvement. Steroid foams also score 80, particularly if the patient’s vote is taken into account. Azathioprine’s score cannot be calculated because there is doubt over its efficacy, but it is potentially 88 if it saves patients with difficult disease from colectomy. We can only guess what an oral non-absorbed steroid would score, but if response rates for relapse were substantially improved, or if corticosteroids could be used as effective maintenance treatment, it could be as high as 95. There are indications that we should ‘watch this space’.

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