Review article: evolving concepts in treatment and disease modification in ulcerative colitis

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SUMMARY

Background
More than two-thirds of ulcerative colitis patients experience at least one relapse over a period of 10 years. Treatments that reduce the likelihood of relapses also reduce the risk of long-term complications.

Aim
To review three topics: the current standard of treatment for ulcerative colitis, evolving concepts in treatment, and disease modification as a treatment goal of the future.

Results
Currently, 5-aminosalicylates are the standard treatment for the induction and maintenance of remission in mild-to-moderate ulcerative colitis patients. Evidence suggests that patients who take oral 5-aminosalicylates regularly are nearly six times more likely to experience regression in disease severity than those who do not. Additional treatment options such as corticosteroids, immunomodulators, biological therapies and ciclosporin are available for moderate-to-severe ulcerative colitis patients, or those who do not respond to 5-aminosalicylate. Surgery becomes pertinent for more than one-third of ulcerative colitis patients during the course of their disease. With the availability of a variety of therapies, advances in surgery and improved management strategies, a better understanding of patient treatment expectations can help improve the quality of care for ulcerative colitis patients.

Conclusions
Disease modification is increasingly becoming a treatment goal in the management of ulcerative colitis. However, long-term studies are needed to examine further the disease modifying role of 5-aminosalicylates.

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The primary goals of therapy in the treatment of ulcerative colitis (UC) are to induce remission of patient symptoms as rapidly as possible and maintain remission on a long-term basis. Reducing the number of relapses, which occurs in 67% of UC patients at least once over a 10-year period, reduces the risk of long-term complications, and improves their quality of life. Long-term studies further suggest that treatment with 5-aminosalicylate (5-ASA) maintenance therapies can reduce the risk of developing colorectal cancer, a complication affecting as many as one in 500 patients. The current standard of treatment is a therapeutic algorithm, which separates patients according to the severity of their disease and response to treatment according to a ‘step-up’ pyramidal approach that begins with the least toxic therapies first (Figure 1).

**5-ASAS IN THE TREATMENT OF UC**

Aminosalicylates, which include mesalazine, sulphasalazine, olsalazine and balsalazide, are the standard treatment for the induction and maintenance of remission in mild-to-moderate UC patients because of their efficacy and safety profiles. Oral 5-ASAs used to treat UC are available in a range of formulations with different release characteristics (Table 1), but have comparable pharmacokinetics in terms of systemic absorption, urinary excretion and faecal excretion of 5-ASA.

Two recent, updated Cochrane meta-analyses of oral 5-ASAs confirmed the efficacy of 5-ASA compared with placebo in the induction and maintenance of remission in UC, with an overall excellent safety profile.

However, direct comparison of the efficacy of different 5-ASAs is made difficult by the lack of a universal definition of response and remission, with different clinical trials using different clinical end points. The currently used methods to define disease activity, clinical response and remission are overlapping, yet varied, translating into markedly different interpretations of clinical trial data. For example, when the ASCEND I and II trial data were analysed using the different end points/definitions of remission from the MATRx and ACT trials, dramatically different remission rates were yielded and varied by almost twofold (Figure 2). Thus, there is a need to standardize outcome measures in UC clinical trials and to re-define remission to make comparisons between trials possible. The practice guidelines formulated by the American College of Gastroenterology have gone some way to standardize clinically useful definitions of UC activity outside of the clinical trial setting.

The optimal dosing of 5-ASA is dependant on the disease severity and disease extent in patients with active UC. Evidence suggests that while ‘standard’ doses (e.g. 2.4 g of mesalazine) are sufficient to treat patients with mildly active UC, many patients with severe disease benefit from higher doses. Oral 5-ASAs can be used alone or in combination with corticosteroids, ciclosporin or immunomodulators such as infliximab.
moderate UC could benefit from treatment with a higher dose of 5-ASA. Results from the ASCEND I and II trials, which compared high (4.8 g/day) and low (2.4 g/day) doses of 5-ASA showed that the higher dose produced significantly greater overall improvement rates than the low dose at 6 weeks in the treatment of moderately active UC (i.e. 72% vs. 59%, respectively; \(P < 0.05\)).\(^\text{16}\) However, this same benefit was not observed in patients diagnosed with mild active UC. In moderately active UC patients, the higher dose of 5-ASA also induced faster relief of symptoms (i.e. stool frequency and rectal bleeding),\(^\text{16}\) and greater endoscopy-measured mucosal healing than the low-dose 5-ASA.\(^\text{17}\) Similarly, subgroup analyses from trials with Asacol and the MMX formulation of mesalazine (mesalamine) have demonstrated that patients with prior 5-ASA or steroid therapy also benefit from the higher, 4.8 g dose.\(^\text{18}\) Furthermore, a retrospective cohort study demonstrated longer periods of remission with higher average daily starting doses of 5-ASA.\(^\text{19}\) Therefore, higher doses of 5-ASA could play a steroid-sparing role.

### 5-ASA and disease modification

During the early stages of UC, relapses are associated with a hastening of disease extension. Evidence suggests that oral 5-ASA treatment may, however, slow the progression of disease. One study showed that patients who regularly used oral 5-ASAs were 5.8 times more likely to experience regression in disease severity than those who did not, supporting a disease modification role of 5-ASA in UC.\(^\text{20}\) In addition, there is evidence to suggest oral 5-ASAs protect against proximal extension of mucosal inflammation in UC.\(^\text{21}\) Further studies are needed to determine the effects of long-term 5-ASA use on disease extent and clinical remission.

### DOES IT MATTER WHICH 5-ASA IS USED TO TREAT ULCERATIVE COLITIS?

The choice of 5-ASAs used in the treatment of UC may be determined by a number of factors other than their pharmacokinetic profile, clinical efficacy and safety profile. Depending on the site of inflammation, one 5-ASA may be more suitable than the other as different formulations/preparations release mesalazines at different sites in the gastrointestinal tract. However, while all of the oral aminosalicylate formulations have demonstrated equal efficacy in extensive and left-sided colitis, patients with distal disease may benefit more from a topical (rectal) preparation of 5-ASA. Most recently, even patients with extensive colitis have been shown to benefit from the addition of a rectal preparation to an oral mesalazine regimen.\(^\text{22}\)

Other differentiating factors for the choice of 5-ASAs include cost-related implications, medication adherence-related factors, such as dosing regimens, patient beliefs and patient preference, as well as physi-

### Table 1. Formulations and release characteristics of oral 5-aminosalicylates (5-ASAs)

<table>
<thead>
<tr>
<th>5-ASA</th>
<th>Formulation</th>
<th>Optimal drug release pH</th>
<th>Site of drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asacol(^a) 400 mg MR tablets</td>
<td>Enteric coated with Eudragit S &gt;7</td>
<td>Terminal ileum and large bowel (colon and rectum)</td>
<td></td>
</tr>
<tr>
<td>Pentasa(^b) 500 mg slow release tablets</td>
<td>Ethylcellulose-coated microgranules to allow slow continuous release</td>
<td>Enteral pH Duodenum to rectum</td>
<td></td>
</tr>
<tr>
<td>Salofalk(^c) 250 mg tablets</td>
<td>Enteric coated with Eudragit L &gt;6</td>
<td>Terminal ileum and colon</td>
<td></td>
</tr>
<tr>
<td>Ipocol(^d) 400 mg tablets</td>
<td>Enteric coated with Eudragit S &gt;7</td>
<td>Terminal ileum and colon</td>
<td></td>
</tr>
<tr>
<td>Mesren(^e) 400 mg MR tablets</td>
<td>Enteric coated with Eudragit S &gt;7</td>
<td>Terminal ileum and colon</td>
<td></td>
</tr>
<tr>
<td>Liálda/Mezavant(^f) 1.2 g tablets</td>
<td>MMX Multi Matrix System technology &gt;7</td>
<td>Terminal ileum and colon</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{a Procter & Gamble Pharmaceuticals Ltd, Egham, Surrey, UK.}
\(\text{b Ferring Pharmaceuticals Ltd, Langley, Berkshire, UK.}
\(\text{c Dr Falk Pharma UK Ltd, Bourne End, Buckinghamshire, UK.}
\(\text{d Sandoz Ltd, Hampshire, UK.}
\(\text{e Ivax Pharmaceuticals Ltd, Cheshire, UK.}
\(\text{f Shire Pharmaceuticals Ltd, Basingstoke, Hampshire, UK.}
cian experience (see articles by Dr A. Robinson and Dr S. Travis and Cdr N. Westwood in this Supplement for additional information).

TREATMENTS OTHER THAN 5-ASAS

The majority of UC patients present with moderate-to-severe disease (80%) rather than mild disease (20%). As per the therapeutic algorithm for UC (Figure 1), additional treatment options other than 5-ASAs are considered for patients with moderate-to-severe disease, or those who do not respond to 5-ASA.

Corticosteroids

Corticosteroids are mainly used for inducing remission in moderate and more severe disease, or for patients who fail to respond rapidly to aminosalicylate therapy. Corticosteroids have been demonstrated to provide rapid relief of symptoms; however, corticosteroids are not used in maintenance therapy, largely because undesirable side effects (e.g. moon face, weight gain and dyspepsia) outweigh the benefits. In addition, in the long term, less than half of patients who require steroids have a prolonged response, approximately a quarter become corticosteroid dependent and nearly one-third of patients require colectomy, suggesting that the need to begin corticosteroid therapy in UC is associated with a poor long-term prognosis. An estimated 15% of UC patients will have a severe relapse of disease within their lifetime that necessitates hospital admission and intravenous corticosteroids.

Azathioprine

As UC patients become dependent-upon or refractory to corticosteroids, treatment options become limited. Often, immunomodulator therapies, such as azathioprine (AZA) or mercaptopurine (6-mercaptopurine) are considered in these patients before surgery. The main role of AZA is as a steroid-sparing treatment and can be used to treat steroid-dependent UC patients. A study of 72 steroid-dependent UC patients treated with either 5-ASA or AZA while receiving concurrent tapering doses of steroids showed that AZA induced significantly better remission rates compared with 5-ASA (i.e. 53% vs. 19%; \( P = 0.006 \)). Once a patient responds to AZA, evidence suggests that long-term therapy will be necessary as Hawthorne et al.'s double-blind study showed that patients randomly switched from AZA to placebo were more likely to relapse than those who continued with AZA therapy (Figure 3). A recent meta-analysis of four trials confirmed that patients who continued with AZA are less likely to experience a relapse than those who received placebo (OR 0.41; 95% CI: 0.24–0.70).

Biological therapy

In patients with moderate-to-severe UC who have not responded to 5-ASAs, steroids or immunomodulators, targeted biological therapies such as infliximab have now become established treatment options. Results from the ACT 1 and ACT 2 studies showed that an induction regimen of infliximab followed by maintenance infusions every 8 weeks was superior to placebo in achieving clinical response and remission, mucosal healing and corticosteroid-sparing effects during 30–54 weeks of therapy.

Ciclosporin

Ciclosporin (CsA) is an important rescue therapy in steroid-refractory patients with severe UC. Evidence shows that 82% of CsA-treated patients responded rapidly (within a week of treatment) compared with no response in placebo-treated patients. Following treatment, patients remain in remission for long periods of time. However, despite the immediate benefit of CsA in inducing a response, this does not correlate with beneficial clinical outcomes in the long term. To establish long-term benefits, patients responding to CsA require AZA maintenance to prevent relapse and/or colectomy. A retrospective study evaluating the outcomes of severe steroid-refractory UC patients treated with CsA over 7 years showed that a high
proportion of patients relapsed after 1 and 3 years (65% and 90%, respectively), with 58% of patients requiring colectomy at 7 years.29

Surgery in UC

Although medical therapy is efficacious, patients with serious UC-related complications, such as dysplasia or cancer, toxic megacolon, perforation or massive haemorrhage will also require colectomy.38 The progressive nature of the disease means that approximately 30–40% of UC patients will require colectomy at some stage in the course of their disease.39

Repeated surgery is sometimes necessary. A population-based cohort showed that approximately 20% of patients who had undergone protocolectomy and ileal pouch-anal anastomosis required at least one additional surgery, and 15% of patients required at least two additional surgeries.40 Whilst surgical techniques have dramatically improved, surgery is still associated with significant complications, e.g. pouch failure, pelvic sepsis, faecal incontinence and a severe reduction in female fecundity.40, 41 Approximately 40% of women have difficulty becoming pregnant after IPAA.42

MANAGEMENT OF UC – WHAT SHOULD PATIENTS EXPECT?

Now, with the availability of a variety of therapies, advances in surgery and improved management strategies, the long-term prognosis of the UC patient has greatly improved over the past decade. A better understanding of the expectations that patients have from their treatment can help improve the quality of care for patients with UC.

The British Society of Gastroenterology have included the patient’s perspectives and expectations into their guidelines for the management of IBD, and outlined what the UC patient should expect from their treatment before, during and after diagnosis (Table 2).26 While these are standards to be striven for, the challenge is balancing these patient needs/expectations with the reality of resource constraints.

FUTURE GOALS OF MANAGEMENT

Although curative options for UC are not on the immediate horizon, disease modification, based on an improved understanding of the pathogenesis of UC, is increasingly becoming a treatment goal in the management of UC.20 To achieve this, patients who will benefit most from early, aggressive medical therapy will need to be identified. As better information regarding risk factors becomes available (including phenotypes and molecular markers), this can allow doctors to identify such patients, and eliminate environmental factors that trigger individual immune responses, or establish patient tolerance to these stimuli. Until such information become available, current knowledge of the various treatment options available, paralleled with a patient-centric approach to management of the disease, remain essential considerations in the optimization of the management of UC patients.

Table 2. The patient’s perspectives and expectations: a summary of what patients should expect26

<table>
<thead>
<tr>
<th>What patients should expect</th>
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<tbody>
<tr>
<td>Before diagnosis</td>
</tr>
<tr>
<td>Quick access to and referral from primary care to specialist Gastroenterologists</td>
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<tr>
<td>At diagnosis</td>
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<tr>
<td>Thoughtful explanation of disease with opportunity for discussion</td>
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<tr>
<td>The offer of suitable written information, audiovisual material and information about patient</td>
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<tr>
<td>support groups and sources of help</td>
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<tr>
<td>Hospital management</td>
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<tr>
<td>Knowledgeable multidisciplinary team</td>
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<tr>
<td>Willingness to refer to specialist centre</td>
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<tr>
<td>Encouragement of self-management</td>
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<tr>
<td>Choice in medical/surgical therapies</td>
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<tr>
<td>Access to dieticians and social workers</td>
</tr>
<tr>
<td>Long-term follow-up</td>
</tr>
<tr>
<td>Continuity of care in primary and secondary care</td>
</tr>
<tr>
<td>Consideration of quality of life issues</td>
</tr>
<tr>
<td>Acknowledgement of physical, emotional and quality of life issues</td>
</tr>
<tr>
<td>Access to second opinions</td>
</tr>
<tr>
<td>Maintain dignity</td>
</tr>
</tbody>
</table>

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