Considerations in the management of ulcerative colitis

Abstract

Ulcerative colitis (UC) is a relapsing chronic disease that has an unpredictable course. This article aims to consider the medical approaches to managing UC, placing emphasis on the use of mesalazine and in particular Salofalk in the management of mild-to-moderate colitis. The article also recognises the importance of supporting patients to identify symptoms of relapse so that timely adjustments to medical therapy can be made to promote symptomatic relief and mucosal healing. In the long term, optimisation of therapy in mild-to-moderate disease is considered to reduce the likelihood of flare; therefore, progression to more expensive and complex therapies can potentially be avoided.

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Ulcerative colitis (UC) is a chronic inflammatory condition of the colon. The disease has an incidence in the UK of approximately 10 per 100 000 annually and a prevalence of around 240 per 100 000, affecting about 146 000 people in the UK (National Institute for Health and Care Excellence (NICE), 2013). It can develop at any age; however, peaks in presentation are noted between the ages of 18 and 45, with a second peak between the ages of 55 and 70 (Royal College of Nursing (RCN), 2007).

Individuals with UC experience diarrhoea, urgency in defecation, faecal incontinence, rectal bleeding, rectal passing of mucus, abdominal pain, anaemia and lethargy. The experience of UC varies by the individual, the extent of their disease and its severity.

Distribution and disease severity

Although the cause of UC is unknown, it is characterised by diffuse mucosal inflammation limited to the colon (*Figure 1*). Inflammation usually begins at the rectum, but it can progress throughout the colon (*Figure 2*); it affects the superficial mucosal layer only, except in severe disease, when the inflammation may be more penetrative (Dignass et al, 2012). It is important to determine the extent and severity of the disease, as this will influence treatment options. Extent is classified according to the distribution of inflammation through the colon, which is usually observed at colonoscopy and based on the Montreal classifications (*Table 1*) (Silverberg et al, 2005). It is worth noting that distribution of the disease can change over time, due to the dynamic nature of inflammatory bowel disease (IBD).

Assessment of disease activity

The Truelove and Witts (1955) classification of disease severity is the most widely used (*Table 2*); other tools, such as the Oxford criteria (Travis et al, 1996), have developed from this in an attempt to offer more sensitive prediction of patient outcomes. However, the Truelove and Witts classification is generally accepted, due to its ability to be integrated into clinical practice.

Treatment of ulcerative colitis

The goal of medical therapy in UC is to relieve symptoms, achieve mucosal healing, improve quality of life and maintain remission. It is important to recognise that the extent of the disease does not dictate the severity of its presentation; for example, proctitis can be severe and extensive colitis can be mild. Prior to commencing treatment, other causes of

Key words

- Adherence
- Disease management
- Inflammatory bowel disease (IBD)
- Mesalazine
- Ulcerative colitis

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symptoms should be considered, and infective causes of UC should be excluded, including cytomegalovirus and *Clostridium difficile*.

The approach to treatment is dictated by clinical severity, disease extent and patient preference. Common approaches include amino-salicylates, corticosteroids, immunomodulators and biologic agents.

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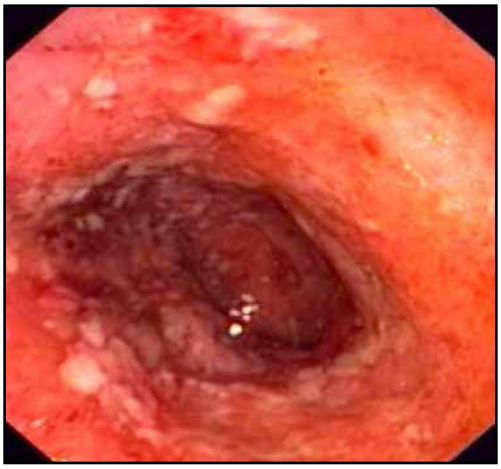

Figure 1. Severe ulcerative colitis

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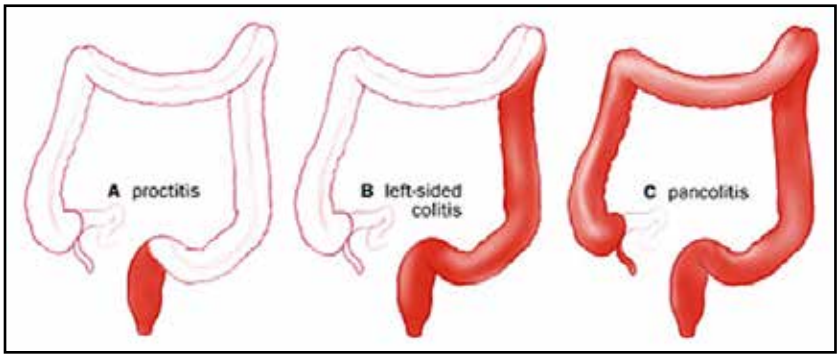

Figure 2. Disease distribution in ulcerative colitis

Table 1. Montreal classification of disease extent

E1	Proctitis	Confined to the rectum
E2	Left-sided colitis	Extends up to the splenic flexure
E3	Extensive colitis	Extends from the rectum to the caecum and involves the entire colon

Source: Silverberg et al (2005)

Table 2. Truelove and Witts classification of disease severity

	Mild	Moderate	Severe
Stools per day	<4	4–6	>6
Blood in stools	Small amount	Present	Present
Pulse	All normal	All normal	>100 bpm
Pyrexia	No	No	Yes
Anaemia	No	No	Yes
ESR	<20 mm/h	20–30 mm/h	>30 mm/h

Key: ESR = erythrocyte sedimentation rate; pyrexia = temperature greater than 37.8 °C
Source: Truelove and Witts (1955)

NICE (2013) acknowledges that there are two main stages in the management of mild to moderate and severe acute UC: the first being the induction of remission and the second maintenance of remission to prevent patients from relapsing. It is worth considering approaches to treatment in terms of disease extent and severity. The European Crohn's and Colitis Organisation (ECCO) also support this approach (Dignass et al, 2012), advocating that treatment of UC should be prescribed according to disease activity and extent, adding that the use of both oral and rectal preparations should be considered.

Standard treatment for mild-to-moderate colitis involves the administration of mesalazine. Mesalazine contains 5-aminosalicylic acid, which works to reduce inflammation in the intestinal wall. Each different brand of mesalazine has a unique coating (*Table 3*). There is considerable debate on the influence of the carrier mode and its impact on inducing remission. The coating is dissolved either by special bacteria only found in the large bowel, or by the acidity (pH) of the large intestine. Different mesalazine preparations are released at different pH levels; some utilise time-dependent release mechanisms that release 5-aminosalicylic acid into different parts of the intestinal tract.

Salofalk granules have a special coating that provides a dual-release mechanism. The release starts at a pH of ≥6, so the active drug delivery starts in the terminal ileum and continues to the distal parts of the colon. Not all patients achieve a pH of 7, so products that release at a pH of ≥7 will not release the active drug at all. Extended release products, such as Pentasa, may release too early in the GI tract, potentially causing 50% of the active drug to be lost before it reaches the affected parts of the colon.

The choice of mesalazine is influenced by cost, with prescribers selecting less costly preparations first line, and preparations that offer once-daily dosing are often adopted, as this can encourage adherence.

Proctitis

Some of the challenges and solutions involved in achieving remission in patients with proctitis are illustrated in the case study provided.

Mesalazine 1 g suppositories are considered the preferred initial treatment for proctitis; however, patient preference should be considered in the first instance, as this will impact adherence with treatment and the long-term likelihood of remission. The patient's preferences, beliefs and understanding regarding therapy should be explored with the patient prior to prescribing (Kane et al, 2001). NICE (2013) recommend the following for proctitis:

- Topical aminosalicylate alone, either as a suppository or an enema
- A combination of oral and topical mesalazine
- Oral mesalazine alone, should the patient have concerns over using rectal preparations.

Key messages that need to be shared with the patient include the rationale for treatment, its potential side effects and the long-term treatment plan. It is worth reflecting on the sustained topical effects of enemas and suppositories within the rectum and communicating this to patients. The use of topical therapy is considered key to inducing remission in proctitis in comparison with oral preparations alone, with remission rates of 60–70% cited (Ford et al, 2011). Furthermore, suppositories are considered more appropriate than enemas in proctitis, as only 40% of foam enemas and 10% of liquid enemas can be detected in the rectum after 4 hours following administration, compared with 12 hours with suppositories (Dignass et al, 2012).

Steroid enemas containing budesonide or prednisolone are occasionally used when there has been limited response to mesalazine preparation. However, their ability to induce mucosal healing is questioned (Dignass et al, 2012), and the long-term effects of steroids should be considered, but there is recent evidence that suggests Budenofalk Foam induces mucosal healing in distal UC (Naganuma et al, 2015).

An important and often overlooked aspect of promoting adherence with treatment is the education of patients regarding the role of suppositories and how to administer rectal therapies (*Figure 3*).

Left-sided colitis

Both NICE and ECCO guidelines recommend the use of a combination of both high-dose oral and rectal mesalazine to induce remission in left-sided colitis. Ford et al (2011) concluded that, as a result of higher mucosal concentrations, combination therapy worked more rapidly than oral mesalazine alone in left-sided colitis, while the likelihood of remission was increased, with remission rates up to 68% quoted, compared with 43% on oral mesalazine alone.

A variety of dosages and preparations are available (*Table 3*). Selection of a particular brand of mesalazine is influenced by local formularies, as well as its acceptability to the patient, cost and

Case study

John is 65, and he has proctitis. He reported opening his bowels 10 times per day with blood and mucus. In an attempt to induce remission, he had previously received Asacol, Pentasa and topical mesalazine, but he did not achieve remission. John had then progressed to immunomodulators in the form of mercaptopurine and methotrexate; however, he was unable to tolerate any of these therapies, due to the development of abnormal liver function. He remained on oral prednisolone.

A sigmoidoscopy was repeated and this demonstrated mild proctitis, and an abdominal X-ray showed proximal constipation. In a last attempt to induce remission, John was put on Salofalk granules (3 g daily) in conjunction with Salofalk suppositories (1 g) and prescribed Movicol (four sachets per day). After 10 days, John reported a good response, and he continued with therapy for a further 3 months. Another sigmoidoscopy at this point showed the disease to be quiescent. His therapy was reduced to 1.5 g of Salofalk granules per day and suppositories as required. Some 2 years later he remained in remission and continued to adjust his therapy as his symptoms dictated.

Table 3. Mesalazine preparations available, with optimal pH and site of drug release

Drug	Optimal pH	Site of release
Asacol MR	>7	Terminal ileum, colon and rectum
Balsalazide	Bacterial responsive	Throughout the colon
Octasa	>7	Terminal ileum and colon
Mezavant XL	>7	Colon
Pentasa	Time dependent	Stomach to rectum
Salofalk	>6	Terminal ileum and colon
Sulfasalazine	Bacterial responsive	Throughout the colon

Image courtesy of Mark Allen Group

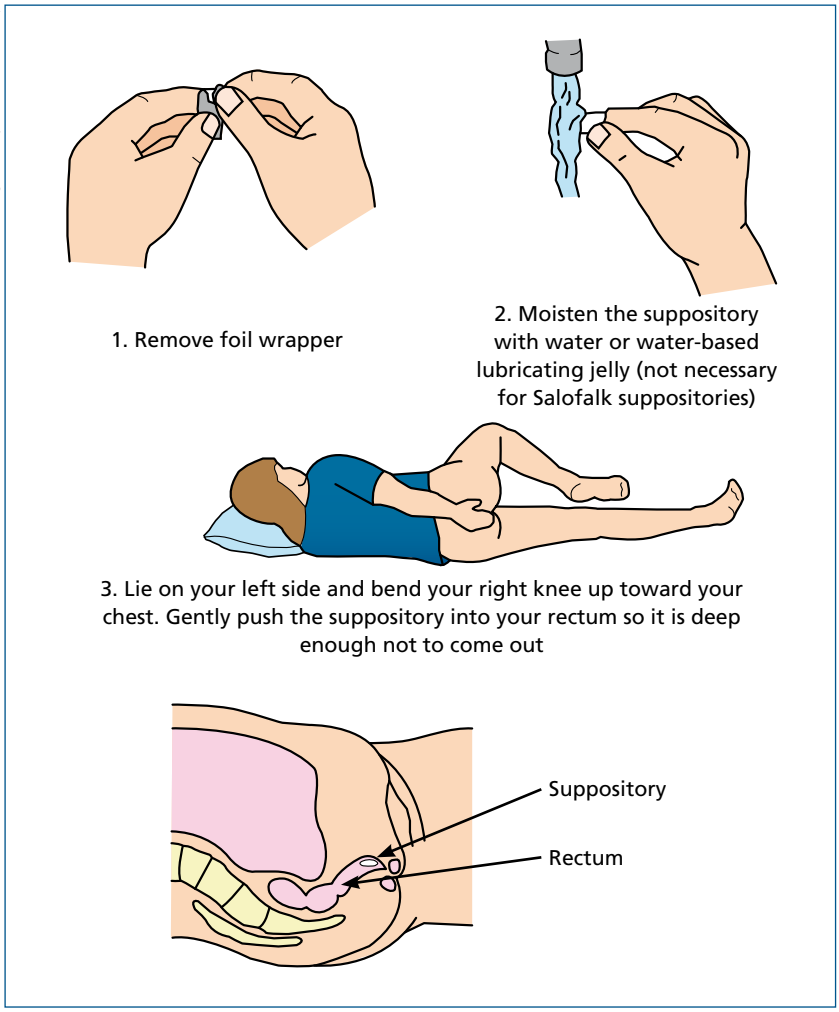

Figure 3. How to insert a suppository

clinical efficacy, which is influenced by a drug's release mechanism, as previously discussed.

There is little difference between once-daily and multiple dosing preparations in terms of remission and response rates, and patients should be educated about response rates. In most preparations, a response is anticipated within 7–10 days, with remission achieved by 8 weeks of treatment. Scintigraphy studies (*Figure 4*) have shown greater left-sided concentrations in the use of Salofalk (Dr Falk) granules in comparison with tablets, suggesting a stronger role in patients with distal UC, although remission and response rates are comparable with those of tablet preparations (Kruis et al, 2009). Anecdotally, the use of Salofalk granules may bypass problems such as proximal constipation, because the small size of the granules allows them to pass through the blocked intestine.

The patient's comfort and willingness to comply with treatment is the single most important consideration in the prescription of topical therapy. There is little evidence to advocate a preference for either foam or liquid enemas. Lower-volume enemas, such as Salofalk, are generally better tolerated by patients (Eliakim et al, 2007). Mesalazine is considered superior to corticosteroid enemas, as mucosal healing is greater with mesalazine preparations, and concerns around long-term steroid usage in terms of bone health should be considered with rectal preparations.

Images courtesy of Dr Falk

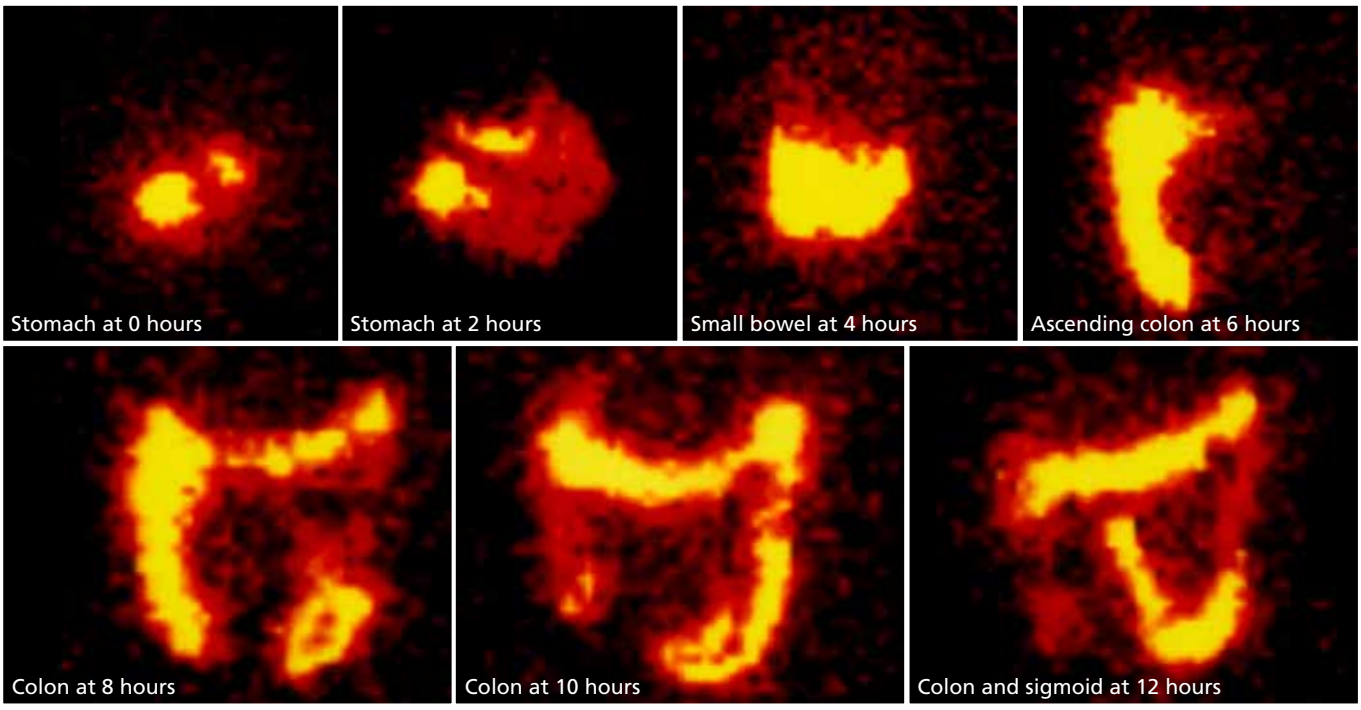

Figure 4. Scintigraphy images representing the release of Salofalk granules over 12 hours (Brunner et al, 2003)

It is essential to discuss administrations technique with patients, as they often hold misconceptions about administering rectal therapy. It is important to reiterate that the patient feels as relaxed as possible and that they lie on their left-hand side, as there is a natural lean of the sigmoid colon to the left, and uptake of the enema is usually more effective as a result. Harris and Leichenstein (2011) suggested that, even with 20 minutes of topical contact, mucosal concentrations of mesalazine were noted for up to 4 hours after administration, concluding that overnight retention is optimal.

Extensive colitis

For the induction of remission with mild-to-moderate extensive colitis, NICE (2013) recommend the use of oral aminosalicylate, and to consider adding a topical aminosalicylate or beclomethasone. ECCO support this adding that mild-to-moderate extensive UC should be treated with oral aminosalicylate greater than 2 g per day (Dignass et al, 2012). Prescribing considerations are similar to left-sided colitis.

Dignass et al (2012) suggested the use of oral prednisolone if patients fail to respond to mesalazine in extensive colitis. Oral prednisolone has been considered a mainstay of treatment for IBD for many years. Truelove and Witts (1955) originally noted its role, suggesting remission rates of 76% after 2 weeks of treatment. Usually, prednisolone is commenced at 40 mg and reduced by 5 mg per week thereafter. It is important that steroid dependence in refractory disease is monitored closely and early immunomodulation is considered in order to reduce adverse events related to prolonged steroid use, including adrenal suppression, osteoporosis and steroid-induced diabetes (NICE, 2013).

More recently, novel preparations have been introduced as alternatives to prednisolone in mild-to-moderate UC, such as beclomethasone and budesonide. Beclomethasone dipropionate is a topical steroid indicated for use in mild-to-moderate UC; it is usually prescribed at 5 mg per day for 4 weeks. Nunes et al (2010) recorded remission rates of 44%, with a further 22% of patients experiencing a reduction in symptoms. Response was noted to be better in extensive colitis in comparison with left-sided colitis.

Cortiment (oral budesonide) is licensed for mild-to-moderate UC, but with only a 17% success rate, it has very limited efficacy.

Table 4. Possible drivers for the development of refractory colitis

- Poor adherence to medication
- Inadequate quantities of active drug delivered to the inflamed mucosa
- Unrecognised complications, such as infection or proximal constipation
- Inappropriate diagnosis, such as irritable bowel syndrome, Crohn's disease or cancer

Source: Dignass et al (2012)

Table 5. Risk factors for non-adherence with mesalazine therapy

- Four or more items on a prescription
- Male
- Single
- Remission for more than 2 years
- Endoscopy within the last 2 years
- Multiple (three or four) daily doses
- Number of tablets (pill burden)

Source: Kane et al (2001)

Supporting patients in the long-term management of colitis

Dignass et al (2012) suggested that there are a number of key areas to explore with patients to prevent the development of refractory colitis and therefore reduce the need to escalate therapy beyond mesalazine to drugs, such as infliximab, that carry greater risks of adverse events and greater financial burdens (*Table 4*).

Adherence in mesalazine treatment

Adherence to mesalazine therapy appears to be pivotal to improving outcome in patients with UC, and this is a key area to address for specialist nurses supporting patients with UC. Kane et al (2001) described adherence rates of approximately 40% in patients managed in outpatient clinics with oral mesalazine, and identified that 90% of patients with an exacerbation of colitis demonstrated poor long-term adherence to medications. They then went on to explore a number of factors that contributed to non-adherence (*Table 5*).

Identification of these risk factors enables clinicians to identify patients who are at risk of non-adherence and tailor their treatment plans appropriately, ultimately improving clinical outcomes and reducing the risk of relapse and progression to immunomodulators and biological therapies.

Treatment plans should be completed in conjunction with the patient, so that health beliefs can be explored regarding diagnosis and

Table 6. Monitoring prior to and during rescue therapy

Cyclosporine	Anti-TNF and vedolizumab
Prior to administration and during therapy • Blood pressure • Low magnesium • Low cholesterol • Seizures • Renal impairment • Liver impairment • FBC, UE, LFT • Consider prophylaxis against opportunistic infections • Cyclosporine levels	**Prior to administration** • Chest X-ray • Quantiferon test • Varicella antibodies • Hepatitis screen • HIV test • FBC, UE, LFT **During therapy** • FBC, UE, LFT

Key: FBC = full blood count; UE = urea and electrolytes; LFT = liver function tests

medical therapy. The clinician can then progress the discussion to inform and educate around the aims and benefits of therapy and its impact on disease control. Throughout this process, patients' understanding of their diagnosis and treatment should be clarified, ensuring acceptability to the patient is acknowledged and assessed. In addition, treatment plans, dosing frequency and formulation may be considered.

A number of studies have been undertaken to compare once-daily dosing against multiple daily dosing for the maintenance of remission in UC. With regards to clinical effectiveness, there is no significant statistical difference between the dosing regimens and the induction and maintenance of remission (Paoluzi et al, 2005; Leifield et al, 2011). However, patient satisfaction was greater with once-daily dosing, and adherence was greater in this group as a result. The advent of newer formulations, such as Salofalk granules, has also reduced pill burden for patients considerably, down from 8–12 tablets per day to a single sachet of medication per day, consequentially improving adherence and clinical response (Kruis et al, 2009). Therefore, once-daily dosing is generally advocated in UC.

Management of adherence is ongoing, and at each consultation with the patient clinicians should reassess and consider adherence as an ongoing issue within the long-term management of UC and evaluate alternate preparations of mesalazine if tolerability or non-adherence remains problematic. Aldulaimi et al (2016) reinforced ongoing assessment in a recent quality, innovation, productivity and prevention (QIPP) review, recognising regular medication review and optimisation of therapy as key to reduction in relapse and healthcare utilisation.

Regarding the optimisation of mesalazine, the following should be considered before stepping up therapy (Taylor and Irving, 2011):

- Dose maximisation
- Patient adherence to therapy
- Extension of treatment duration
- Combination of oral and rectal therapy
- Switching mesalazine brands.

Severe colitis of any extent

Acute severe ulcerative colitis (ASUC) is a potentially life-threatening scenario. Truelove and Witts (1955) described how, before the use of corticosteroids, 75% of patients with ASUC died. It is an important reflection of the national IBD audit (Royal College of Physicians (RCP), 2008) to consider that this has been reduced to less than 2.9% with changes in approaches to care and the advent of new medical therapies in UC.

Corticosteroids are the mainstay of treatment for severe colitis. Hydrocortisone is usually given intravenously for 3 days initially, with close assessment of response and monitoring for deterioration. Assessment should include:

- Daily full blood count (FBC), urea and electrolytes (UE) and liver function tests (LFT) to assess for anaemia, infection and deterioration in kidney and liver function
- Checking of stool cultures for infection
- Monitoring of faecal calprotectin for increasing trends in inflammation
- Abdominal X-ray to assess for toxic megacolon and proximal constipation
- Unprepped flexible sigmoidoscopy to confirm disease activity (completed cautiously due to increased risk of perforation).

Patients who respond well should have their mesalazine maximised and intravenous steroids switched to an oral reducing course, and immunomodulating therapy should be given early consideration if appropriate.

Patients who fail to respond should be referred to the surgical teams. The IBD standards (RCP, 2013) recommend that a multidisciplinary approach is key, with close working of medical and surgical teams to improve therapeutic outcomes. On or around day 3, it is essential that rescue therapy or surgical intervention is considered in collaboration with the patient. Increased bowel frequency and raised inflammatory markers on

day 3 have associated predictive colectomy rates of between 55 and 85%.

Rescue therapy is usually in the form of either cyclosporine or anti-TNF therapy (NICE, 2013), the aim being either to bridge the patient until the immunosuppressants have been given sufficient time to induce remission or to induce remission in a patient who has failed azathioprine. Williams et al (2016) compared the use of cyclosporine and infliximab in the management of steroid-resistant UC, finding that both were effective in the induction of remission; the incidence of surgery and adverse events were identical for both treatment groups. They also concluded that cyclosporine was a more cost-effective treatment in the UK because of the drug acquisition costs of infliximab. Despite this study, clinicians tend to opt for infliximab first line. This is anecdotally attributed to the lack of long-term data to reassure clinicians regarding long-term side effects and outcomes, and, at present, its use is not supported in pregnancy.

A more recent introduction to the management of UC is vedolizumab, which is the first gut-specific monoclonal antibody. Its role is an α4β7 integrin-receptor antagonist that aims to induce remission. NICE recommends the use of vedolizumab in UC for patients with severely active disease. This recommendation is based on the outcomes of GEMINI 1 (Feagan et al, 2013) studies that clearly demonstrate its role in the induction and maintenance of remission in patients with UC, including those with prior anti-TNF exposure. The use of this medication and its place in clinical practice continues to emerge; however, there is little doubt that it will become a mainstay of treatment for IBD over the coming years.

Counselling and preparing patients for therapy is key to the prevention and early detection of side effects. In addition, the risks and benefits of anti-TNF, cyclosporine or vedolizumab should be discussed with the patient, reiterating the persistent risk of surgery while their colitis remains severe, and that even after initial doses their condition should be monitored closely for potential side effects, including headaches, nausea, upper-respiratory-tract infection, abdominal pain, skin rash, diarrhoea, tuberculosis, malignancy and congestive heart failure (Behm and Bickston, 2008).

The signs and characteristics that should be monitored before and during rescue therapy are listed in *Table 6*. If surgery is necessary and there is time, patients should be referred to stoma care to explore the implications of having a stoma and provided with insight into how this would affect them on a daily basis.

Conclusion

Therapeutic choices in UC need to be tailored to the patient, the extent of the disease and its clinical severity. It is important that clinicians are appraised of NICE and ECCO guidelines to steer their decision making. It is essential that clinical staff clearly understand the different treatment options for the different extents of UC, so that they can integrate them into treatment plans.

Therapies and approaches are changing dramatically, with new biological agents on the horizon, which are likely to have a significant impact on the health economy. Therefore, optimisation of mesalazine has a significant role in the reduction of complications and the progression of disease activity.

Although medical management is the mainstay of IBD management, a holistic approach to management is necessary, particularly as UC affects patients early on their lives, and the over-arching aim of management is for patients to achieve life goals and limit the impact of diagnosis. **GN**

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