Recommended drug therapies for inflammatory bowel disease

CHRISTOPHER WHITE, AMIT THAKOR AND RISHI GOEL

The treatment of inflammatory bowel disease (ulcerative colitis and Crohn's disease) has been revolutionised in recent years with the advent of biological therapies. This article discusses the current role of both conventional and biological treatments in the management of these conditions.

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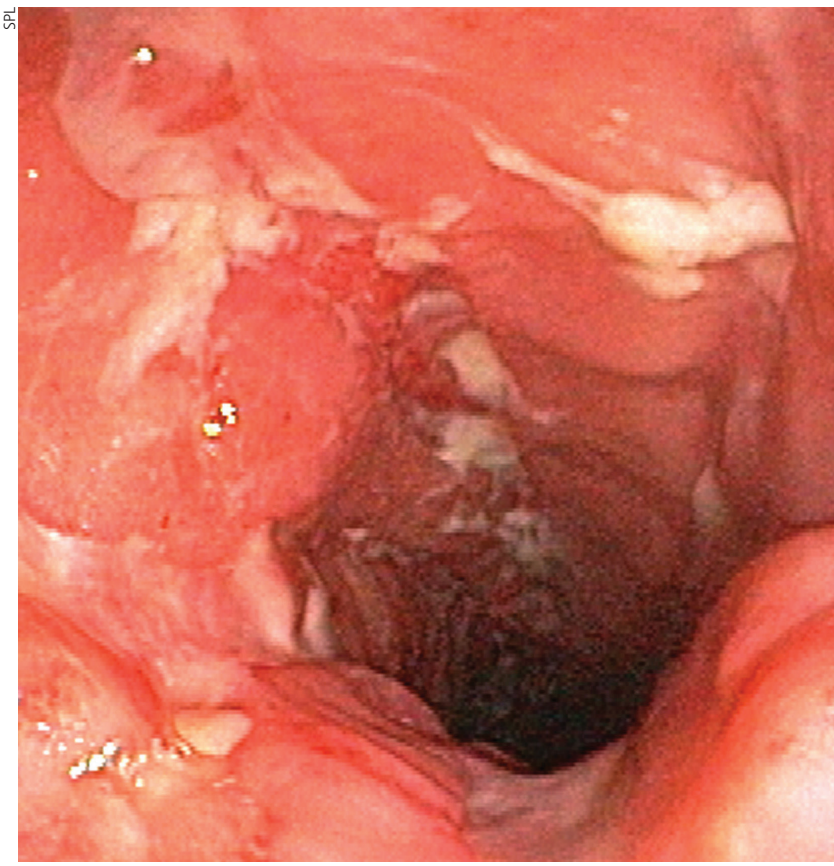

The inflammatory bowel diseases (IBD) ulcerative colitis and Crohn's disease are characterised by chronic inflammation of the gastrointestinal tract. There are approximately 240,000 patients with IBD in the UK, with a reported prevalence of approximately 400 per 100,000 population.[1] The majority of these patients are diagnosed with either ulcerative colitis or Crohn's disease with approximately 5% of cases labelled as 'IBD-unclassified' (IBD-U).[2]

Ulcerative colitis is characterised by continuous inflammation beginning in the rectum and involving the colon to a variable extent. Chief symptoms are rectal bleeding and diarrhoea. Crohn's disease differs in that it is defined by the presence of patchy, discontinuous inflammation, which can affect any part of the gut, but most commonly involves the ileocaecal region (see Figure 1). Granulomatous inflammation is a key feature in Crohn's disease and inflammation can also penetrate through the bowel wall leading to fistulising disease as well as bowel stricturing.

The estimated lifetime risk for surgery remains high, with rates up to 75% for Crohn's disease and 20–30% for ulcerative colitis, dependent on disease severity, behaviour and location.[2] In ulcerative colitis, there has been a general reduction in the risk of colectomy and inpatient death for emergency admissions in English hospitals over the past decade.[3]

The presentation and diagnosis of IBD is based on the correlation of clinical, biochemical, radiological, endoscopic and histological findings. Faecal calprotectin (a test detecting neutrophil-derived protein in the stool) is a marker of inflammation and a useful discriminant between IBD and functional gut disorders such as irritable bowel syndrome,[4] which can help guide assessments and referrals from primary care.

In recent years, IBD treatment has been revolutionised by the advent of biological therapies – complex drugs developed from naturally occurring proteins. The first biological therapies to be used in IBD were anti-TNF alpha monoclonal antibodies.

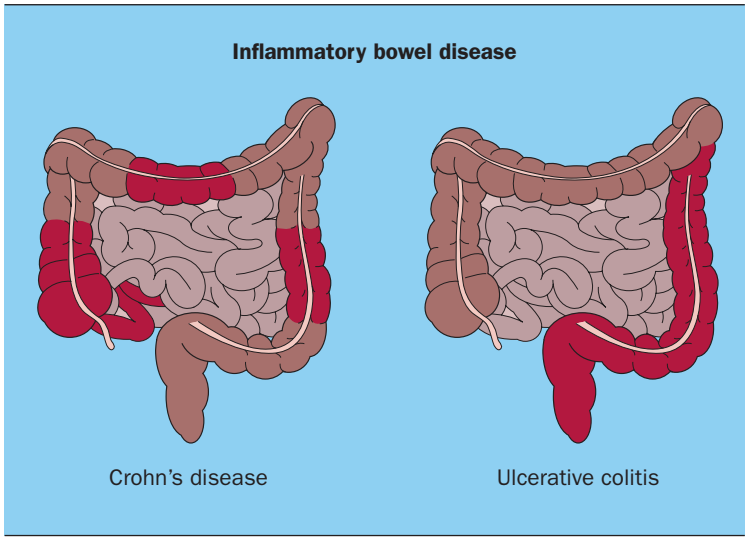

Figure 1. Areas of the gastrointestinal tract affected in Crohn's disease and ulcerative colitis

There are increasing numbers of biological drugs coming to the market, with different modes of action. Generally, biological drugs block a specific molecule within the inflammatory process that occurs in IBD. They improve quality of life and reduce emergency hospital presentations as well as reducing the protracted use of steroids with their associated side-effects. However, biological therapies are high-cost drugs, have to be delivered by injection (intravenous or subcutaneous), and are not without side-effects. For these reasons, biological therapies require surveillance and effective monitoring (such as drug levels and detection of antibodies against the drug).

Disease assessment

Current NICE guidelines outline treatments for ulcerative colitis and Crohn's disease both in terms of inducing and maintaining remission of disease. Ulcerative colitis severity can be assessed on a clinical basis by using a partial Mayo score (see Table 1). Crohn's disease severity can be assessed using the Harvey-Bradshaw Index (see Table 2) with higher scores correlating with increasing disease severity. Conventional drug treatments are used in mild to moderate IBD, and biological agents for moderate to severe IBD (see Tables 3 and 4).

Treatment of ulcerative colitis

Conventional drug treatments in mild to moderate ulcerative colitis

When determining the appropriate treatment, both the location and severity of the disease should be considered. To induce remission in ulcerative colitis patients with proctitis or proctosigmoiditis, topical (rectal) mesalazine or corticosteroids are used. With more extensive ulcerative colitis involving most or all of the colon, oral mesalazine, or oral prednisolone in more severe disease, is used to induce remission. Mesalazine is also an effective maintenance therapy in ulcerative colitis. If mesalazine fails to maintain remission and repeated steroid doses are necessary, then steroid-sparing therapy such as azathioprine or mercaptopurine (thiopurines) may be effective in maintaining remission. Rarely, more severe or treatment-resistant ulcerative colitis can be treated with tacrolimus or ciclosporin; however, these are not long-term therapeutic options and require careful monitoring.

Biological drugs in moderate to severe ulcerative colitis

Studies have demonstrated the efficacy of anti-TNF alpha therapies adalimumab,[7] golimumab[8] and the chimeric antibody infliximab in moderate to severe ulcerative colitis.[9] Indeed, perhaps driven by ulcerative colitis being considered more as a progressive disease rather than a disorder with periodic flares,[10] the threshold for introduction of biological therapy is being lowered.[11]

NICE has approved the use of biological therapy for moderate ulcerative colitis since 2015 and acute severe ulcerative colitis since 2008. The 2015 NICE guidance (TA329) advocates that the choice of treatment between anti-TNF alpha therapies be made on an individual basis following discussion between the patient and clinician. The least expensive option should be chosen if more than one treatment is suitable but practically, this is greatly influenced by local funding agreements. Furthermore, the recent availability of infliximab biosimilar drugs has allowed for increased market competition and cheaper alternative options to the originator compound (Remicade). Switching from originator infliximab to biosimilar infliximab has enabled cost savings and greater access to treatment for patients. It is expected that biosimilar adalimumab will be available by the end of 2018, which should allow for increased competition and lower prices. Such changes may mean that biological drugs are utilised earlier in the treatment pathway, moving away from the current step-up approach.

Treatment with a biological drug should only continue if there is evidence of response (considering symptoms, clinical scores, biomarkers and, where possible, endoscopic findings) with ongoing reassessment of the clinical picture at least annually. Monitored treatment withdrawal can be considered for those in stable remission but with the caveat that those who relapse following treatment cessation have the option to restart therapy if their disease flares.

Considerations with anti-TNF alpha therapies

Anti-TNF alpha drugs are potent immunosuppressors. Before initiating an anti-TNF alpha drug, caution should be taken to screen for tuberculosis (reactivation risk), hepatitis B (reactivation risk) and hepatitis C. Active infections (*eg* perianal abscess) should be treated beforehand. Anti-TNF alpha therapy is best avoided in patients with current or past cancer since there is a risk of reactivation. Anti-TNF alpha drugs can exacerbate heart failure, and rarely cause demyelination.

Vedolizumab for ulcerative colitis unresponsive to anti-TNF alpha therapy

Vedolizumab is a monoclonal antibody that targets the $\alpha_4\beta_7$ integrin, acting as an inhibitor of adhesion molecules, thus

selectively preventing leucocyte infiltration into the gastrointestinal submucosa[12] with a resultant gut-selective anti-inflammatory effect. A Cochrane review concluded vedolizumab is superior to placebo as an induction and maintenance therapy for ulcerative colitis[13] and, as recommended by NICE (TA342), vedolizumab may now be offered for moderate to severe active ulcerative colitis, albeit with the same caveats of the anti-TNF alpha therapies. Compared with anti-TNF therapies, vedolizumab takes longer to achieve an initial clinical response and is more gut-selective in its mode of action. It has demonstrated similar benefits with regards to durable response and mucosal healing.[14] The predominant side-effects can be the development of nasopharyngitis and, less commonly, arthritis.[15,16]

Treatment of Crohn's disease

Crohn's disease can be classified by both its activity and its location (*eg* the presence of perianal disease) but can also be classified by its behaviour, relating to it causing transmural inflammation (*eg* stricturing or penetrating disease). Most commonly, Crohn's disease affects the distal small bowel and the colon (ileocaecal region), although it can affect any part of the gastrointestinal tract, differentiating it from ulcerative colitis in this regard. Crohn's disease is highly heterogeneous and may progress from an inflammatory phenotype to inflammation with fibrosis and strictures.

Conventional drug treatments in mild to moderate Crohn's disease

Corticosteroid therapy may be effective in inducing remission in patients with a first presentation of Crohn's disease or a single inflammatory exacerbation of Crohn's disease in a 12-month period. However, steroid prescribing is avoided where possible as it does not have a significant long-term disease-modifying effect and is associated with considerable side-effects. Oral budesonide is an effective option in terminal ileal Crohn's disease. It is rapidly metabolised and is predominantly released in the terminal ileum with minimal systemic absorption. While an effective bridging treatment, there is no role for steroids in the maintenance of remission. The role of mesalazine is controversial, with the 2016 Cochrane review[17] offering conflicting findings to the 2017 review of Coward *et al*,[18] disputing the efficacy of mesalazine in Crohn's disease. Overall, mesalazine therapy does not appear to be an effective treatment in Crohn's disease.

Thiopurines such as azathioprine and mercaptopurine are indicated as steroid-sparing therapy for patients who have two or more exacerbations in 12 months requiring steroid treatment. However, thiopurines can take up to three months to reach significant efficacy and so their role is as maintenance therapy.

Biological drugs in moderate to severe Crohn's disease

Biological therapies are indicated for moderate to severe Crohn's disease. There are currently two anti-TNF alpha drugs in the UK for the treatment of Crohn's disease: infliximab and adalimumab. They are effective in inducing and maintaining remission and can be effective in healing fistulising and stricturing disease. As with ulcerative colitis, NICE guidance (TA187) recommends that the disease status should be reassessed after 12 months to determine the ongoing need for treatment and to consider treatment withdrawal if the patient is in remission. Although generally effective, up to approximately 20% of patients may lose response to treatment every year, usually secondary to antibody production against the biological agent. In those who lose response, therapeutic monitoring of drug and antibody levels can determine whether antibody production is mediating the loss of response or whether dose intensification may be required if drug levels are subtherapeutic.

There is still divergent opinion about when to commence biological treatment, although generally a step-up approach to treatment is taken. Severe cases such as patients with

0–4 = Mild 5–8 = Moderate 9–12 = Severe

Score interpretation:

- The higher the score, the more severe the case of ulcerative colitis
- Scores should be compared to previous patient scores to assess disease behaviour/response
- Mucosal appearance at endoscopy is not included in the partial Mayo score (maximum partial score = 9)

Measure	Severity	Score
Stool frequency per day	Normal number of motions	0
	1–2 more than normal	1
	3–4 more than normal	2
	5+ more than normal	3
Rectal bleeding	None	0
	Streaks of bloods with <50% of bowel motions	1
	Obvious blood in stool most of the time	2
	Blood alone passed	3
Physician's Global Assessment	Normal	0
	Mild disease	1
	Moderate disease	2
	Severe disease	3
Endoscopic findings	Normal or inactive disease	0
	Mild disease	1
	Moderate disease	2
	Severe disease	3

Table 1. Mayo score for assessing ulcerative colitis severity[5]

penetrating or perianal disease may benefit from top-down treatment; that is, early use of biological therapy to aim for mucosal healing and to avoid/delay surgery if possible. Where possible, anti-TNF alpha treatment is given in combination with an immunosuppressant such as a thiopurine. Such combined therapy is beneficial, particularly in those with complicated Crohn's disease, earlier in the disease course.[19] This was verified in the SONIC trial,[20] which found Crohn's disease patients on combination infliximab and azathioprine therapy had higher rates of steroid-free remission. Specific factors that may favour combination therapy include perianal disease, surgical history and more extensive disease but treatment should be tailored to the individual.[21]

Newer biological drugs in Crohn's disease

In 2015, NICE's technology appraisal guidance (TA352) approved the use of vedolizumab for moderate to severe active Crohn's disease if anti-TNF alpha treatment has failed (lack or loss of response), cannot be tolerated or is contraindicated. Vedolizumab has been found to more effective than placebo in Crohn's disease patients irrespective of anti-TNF alpha treat-

Symptom	Severity	Score
General well-being	Well	0
	Slightly poor	1
	Poor	2
	Very poor	3
	Extremely poor	4
Abdominal pain	None	0
	Mild	1
	Moderate	2
	Severe	3
Diarrhoea		1 for each liquid stool per day
Abdominal mass	None	0
	Dubious	1
	Definite	2
	Definite with tenderness	3
Complications	Arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcer, anal fissure, new fistula or abscess	1 for each complication

Table 2. Harvey-Bradshaw Index for assessing Crohn's disease severity[6]

Ulcerative colitis	Crohn's disease
Steroids Mesalazine Thiopurines Methotrexate Ciclosporin Tacrolimus	Steroids Antibiotics Enteral nutrition Thiopurines Methotrexate

Table 3. Summary of current conventional treatments for ulcerative colitis and Crohn's disease

ment history[22] and has been found to be a safe and effective treatment in routine clinical practice.[23] Currently, however, the cost of this $\alpha_4\beta_7$ integrin antibody is significantly greater than that of infliximab or adalimumab, and it is less frequently prescribed as a first-line agent. Additionally, vedolizumab has a relatively slower onset of action and takes longer to be effective.[24]

More recently (in July 2017), ustekinumab was recommended by NICE (TA456) as an option for treating moderate to severe active Crohn's disease in adults who previously had an inadequate response to, lost response to or could not tolerate conventional therapy or anti-TNF alpha treatment. Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin (IL)-12 and IL-23 and is also used to treat plaque psoriasis and psoriatic arthritis. Intravenous ustekinumab is superior to placebo in inducing a response, and subsequent subcutaneous ustekinumab can maintain remission in patients who had a clinical response to induction therapy.[25,26] Once again, caution should be taken to screen patients for tuberculosis and to ensure there are no active infections at the time of commencing treatment.

Conclusion

IBD is a chronic disease associated with considerable morbidity impacting on physical and mental health. Early diagnosis and intervention should be targeted with a multidisciplinary approach to care. Biological treatments are high-cost parenterally-administered drugs that can induce and maintain remission in moderate to severe ulcerative colitis and Crohn's disease. They can prevent or reduce the need for steroids and surgery. The increasing role of therapeutic drug monitoring with assays to measure drug levels and antibody formation appears helpful in detecting loss of response and achieving optimal benefit from treatment. Newer biological agents such as vedolizumab and ustekinumab are also included in NICE guidelines and offer treatment via different pharmacological mechanisms to the more established anti-TNF alpha therapies.

The availability of biosimilar adalimumab later this year will lead to a fall in costs, greater competition and improved patient access. There are also many new therapies in the pipeline, with the next classes of drugs including janus kinase (JAK) inhibitors and SMAD7 antisense oligonucleotides.[27] These drugs may offer efficacy rates and safety profiles comparable or greater than currently available biological agents, and many will be oral therapies. The possibility of combining drugs with different mechanisms of action will be an exciting prospect and may lead to higher efficacy rates.

Drug class	Ulcerative colitis	Crohn's disease
Anti-TNF alpha	Infliximab (iv) Adalimumab (sc) Golimumab (sc)	Infliximab (iv) Adalimumab (sc)
Anti-integrin	Vedolizumab (iv)	Vedolizumab (iv)
Anti-IL-12 and IL-23		Ustekinumab (iv and sc)

Table 4. Summary of current biological therapies for ulcerative colitis and Crohn's disease

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Dr White is a Gastroenterology Trainee Registrar, Dr Thakor is a Gastroenterology Trainee and Dr Goel is a Consultant Gastroenterologist at Kingston Hospital, Kingston-upon-Thames