The role of biologics in the treatment of patients with inflammatory bowel disease

ABSTRACT

The treatment of inflammatory bowel disease has changed dramatically over the last two decades. The arrival of infliximab as the first biological medicine for inflammatory bowel disease revolutionized its management. Since then the armamentarium of biological medicines for inflammatory bowel disease has grown to five drugs in three different classes. This article highlights the different mechanisms of action and describes the key evidence for their use including drug safety profiles. Furthermore it highlights the current National Institute for Health and Care Excellence recommendations for biological therapy in inflammatory bowel disease and discusses pending changes to the classic treatment algorithms in light of emerging evidence.

The term inflammatory bowel disease refers to ulcerative colitis and Crohn's disease. These are chronic, relapsing, inflammatory conditions affecting the gastrointestinal tract (Mowat et al, 2011). Ulcerative colitis causes mucosal inflammation which starts in the rectum and extends proximally, only affecting the large bowel, while Crohn's disease causes transmural inflammation that can affect any part of the gastrointestinal tract. Crohn's disease is also associated with abscesses, fistulas and stricturing disease (Mowat et al, 2011). Symptoms of diarrhoea and rectal bleeding are common to both, as are extra-intestinal manifestations such as skin rashes, arthritis and eye involvement, but Crohn's disease is more likely to be associated with abdominal pain and weight loss.

The prevalence of inflammatory bowel disease in developed countries is estimated to be 0.5–1%, indicating that between 300 000 and 600 000 people in the UK are likely to be affected (Molodecky et al, 2012). The rising incidence coupled with the young age of onset means that treatment of inflammatory bowel disease has significant cost implications. The aetiology of inflammatory bowel disease is not yet fully understood. Current theories suggest that a combination of genetics, environmental factors such as smoking and the interaction of the immune system with the gut microbiome play a role. Given the strong role of the immune system, the mainstay of advanced treatment for inflammatory bowel disease hinges on immunosuppression.

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Non-biological (conventional) therapy of inflammatory bowel disease

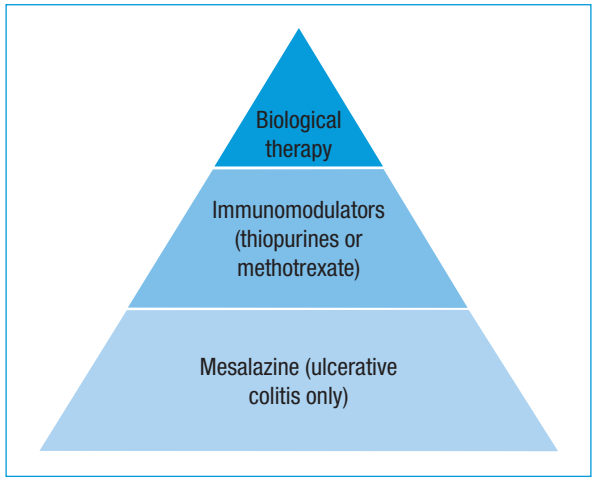
Treatment of inflammatory bowel disease needs to take the type, severity and extent of disease and patient preferences into account. Oral and/or topical mesalazine are first-line therapy for mild to moderate ulcerative colitis (Mowat et al, 2011), but there is no role for mesalazine in Crohn's disease. Corticosteroids are the treatment of choice for flares in both ulcerative colitis and Crohn's disease. Budesonide offers a more gut-directed therapy with fewer side effects. Immunomodulator therapy with thiopurines (ulcerative colitis and Crohn's disease) or methotrexate (Crohn's disease only) is indicated for patients with moderate to severe disease or those requiring prolonged or repeated treatment with corticosteroids (Mowat et al, 2011).

Classic treatment algorithms followed a step-up approach from mesalazine (ulcerative colitis only) to immunomodulatory and on to biologics for those failing to respond (*Figure 1*). Alternative treatment approaches are discussed later on (*Figure 2*).

Biologic therapy

Biological therapies are substances which are made from living organisms to target specific molecules. These include monoclonal antibodies that can be directed at targets

Figure 1. Classical step-up therapy.



such as tumour necrosis factor-alpha (TNF-α). Because of their protein structure monoclonal antibodies need to be administered parenterally and oral applications are not available. This article now discusses the biologics separately by class of action and disease indication.

Anti-tumour necrosis factor therapy

Of the many cells and cytokines involved in the pathogenesis of inflammatory bowel disease, T helper 1 and 17 cells (Th1 and Th17) are important pro-inflammatory cytokines that lead to an increase in circulatory and tissue levels of TNF-α (Corte et al, 2012). There are currently three anti-TNF-α monoclonal antibodies licensed for treatment of inflammatory bowel disease in the UK: infliximab, a chimeric human–murine monoclonal antibody administered by intravenous infusion (8-weekly during maintenance), adalimumab, a fully humanized antibody administered by fortnightly injection and golimumab, a fully human monoclonal IgG1 antibody administered by monthly injection. These inhibit TNF-α and in so doing limit the promotion of inflammatory pathways – this induces and maintains remission of ulcerative colitis and Crohn's disease as well as causing mucosal healing (Kim and Cheon, 2017).

Ulcerative colitis

The key evidence for infliximab, adalimumab and golimumab stems from global, multicentre, double-blind randomized controlled trials of patients with Mayo scores of 6–12 who had failed conventional treatments; mostly these patients were naïve to anti-TNF agents.

The ACT1 and ACT2 trials showed infliximab to be superior to placebo in inducing and maintaining remission in patients with ulcerative colitis and demonstrated mucosal healing (Rutgeerts et al, 2005). Clinical response at week 8 was higher in the infliximab group (69% *vs* placebo 37%, $P<0.001$, in ACT1 and 65% *vs* 29%, $P<0.001$, in ACT2). This response was maintained at week 30 and week 54. In ACT1 clinical response was 54% for infliximab patients *vs* 20% for placebo at week 54 (Rutgeerts et al, 1999). The UC-SUCCESS study showed that patients who had infliximab and azathioprine combination therapy were more likely to be in steroid-free remission at week 16 (39.7% *vs* 22.1%, $P=0.017$) and had the greatest improvement in their quality of life scores compared to infliximab alone (Panaccione et al, 2014). Combination therapy may have synergistic effects but also reduces anti-drug antibody formation that can reduce efficacy (Selinger et al, 2017).

The ULTRA 1 and ULTRA 2 trials compared adalimumab to placebo in ulcerative colitis. These trials found rates of clinical remission were higher in the adalimumab group (16.5% *vs* placebo 9.3% at 8 weeks, $P=0.019$, and 17.3% *vs* 8.5% at 52 weeks, $P=0.004$). However, rates of remission were lower for patients who had failed to respond to a previous TNF-α treatment (Sandborn et al, 2012).

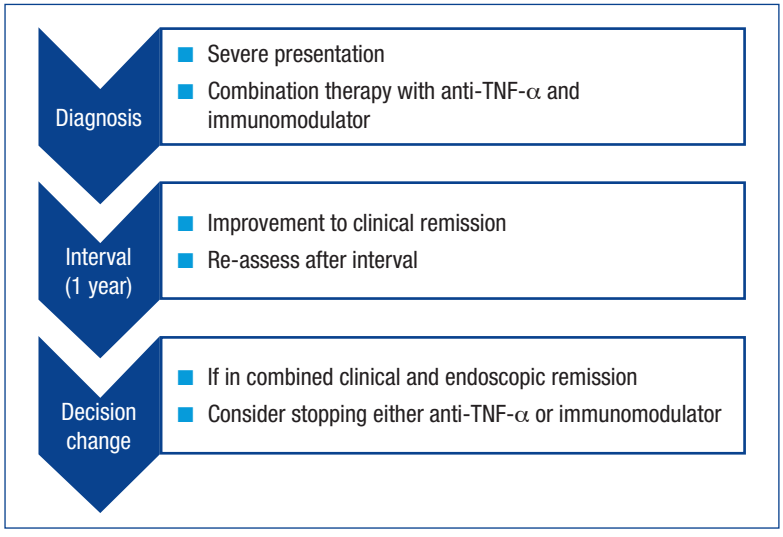


Figure 2. The step-down approach. TNF-α = tumour necrosis factor-alpha.

In the PURSUIT-SC trials, golimumab was associated with better clinical remission, mucosal healing and quality of life compared with placebo in anti-TNF-naïve patients. Clinical remission was attained in 17.8% in the golimumab group at 6 weeks compared to 6.4% in the placebo ($P<0.0001$), and mucosal healing was seen in 42.3% compared to 28.7% in the placebo group (Sandborn et al, 2014). This was sustained to week 54 with 27.8% of patients remaining in clinical remission in the 100 mg golimumab group *vs* 23.2% in the 50 mg golimumab group *vs* 15.6% in the placebo ($P=0.004$ and $P=0.122$ respectively) (Sandborn et al, 2014).

Crohn's disease

The ACCENT 1 and 2 trials showed that maintenance infliximab infusions were superior to placebo for the treatment of Crohn's disease. Remission rates at week 30 were 21% for placebo *vs* 39% for 5 mg/kg infliximab week 2, 6 and then 8-weekly *vs* 45% for infliximab 5 mg/kg at weeks 2 and 6 followed by 10 mg/kg 8-weekly. They also showed median time to loss of response was 38 weeks for the infliximab groups (Hanauer et al, 2002). Combination therapy with azathioprine leads to better results in treatment-naïve patients with Crohn's disease than either therapy alone as demonstrated by the SONIC study (Colombel et al, 2010).

Several trials have established the utility of adalimumab for the treatment of Crohn's disease. The CLASSIC 1 trial compared three different adalimumab dosing regimens with placebo for treatment of Crohn's disease in anti-TNF-naïve patients. This showed remission rates at week 4 were 24% in the 80 mg/40 mg group, 36% in the 160 mg/80 mg group and 12% in the placebo group (Hanauer et al, 2006). Finally, the CHARM trial showed that rates of remission were higher in the adalimumab 40 mg alternative weekly (40%) and 40 mg weekly groups (47%) compared with placebo (17%) at week 26 and week 56 (36%, 41% and 12% respectively; $P<0.001$) (Colombel et al, 2007).

Indications and pre-biologic screening

In the UK, infliximab, adalimumab and golimumab (*Table 1*) are licensed for treating patients with moderately to severely active ulcerative colitis whose disease has failed to respond adequately to conventional therapy. In patients with acute severe colitis infliximab is the biologic of choice if rescue therapy after failure of intravenous corticosteroids is needed. Infliximab and adalimumab are the current anti-TNF therapies licensed for use in Crohn's disease, but only infliximab has a licence for use in patients with fistulating Crohn's disease. To avoid infective complications during therapy it is advised that all patients undergo screening before initiation of biologic therapy – current UK recommendations for screening tests include the exclusion of hepatitis B and, by serology testing, the exclusion of latent tuberculosis (by chest X-ray and interferon gamma relays assays), and confirmation of varicella status.

Common side effects

Side effects common to all the anti-TNF agents include increased risk of infection including opportunistic infections, activation of latent tuberculosis or acquisition of primary tuberculosis, worsening of hepatitis B and an increased risk of malignancies including lymphoma. Injection site reactions or infusion reactions are not infrequent but are simply managed with antihistamines, and anaphylaxis is thought to occur in fewer than 1% of infusions. Neurological complications such as demyelinative conditions and autoimmune conditions such as lupus-like syndromes have also been seen.

Current developments with anti-TNF agents

Owing to the expiry of patents, biosimilar medicines that closely match the originator product have become available for infliximab and adalimumab. As biologics are large and complex protein structures produced by living cells biosimilar medicines are not 100% chemically identical to the originator but they have been shown to be equally effective, and switching from originator to biosimilar products was associated with maintenance of clinical response (Ratnakumaran et al, 2018). The advent of biosimilars has lead to a significant price drop with associated cost reduction to the health service. While up to 30% of patients experience a secondary loss of response after initial response to anti-TNF therapeutic drug monitoring of drug trough levels and anti-drug antibodies can help overcome loss of response (*Table 2*) by dose adjustments (+/- addition of immunomodulator) or tailored switches within or out of class (Selinger et al, 2017).

Table 1. Overview of licenses and NICE recommendations for biological therapy in inflammatory bowel disease

		Ulcerative colitis	Crohn's disease
Anti-TNF	Infliximab	Licensed and NICE recommended as first-line biological therapy	Licensed and NICE recommended as first-line biological therapy
	Adalimumab	Licensed and NICE recommended as first-line biological therapy	Licensed and NICE recommended as first-line biological therapy
	Golimumab	Licensed and NICE recommended as first-line biological therapy	Not licensed for Crohn's disease
Anti-integrin	Vedolizumab	Licensed and NICE recommended as first-line biological therapy	Licensed as first-line biological therapy NICE recommended after failure, intolerance of or contraindication to anti-TNF therapy
Anti-IL23	Ustekinumab	Not licensed for ulcerative colitis	Licensed and NICE recommended as first-line biological therapy

NICE = National Institute for Health and Care Excellence; TNF= tumour necrosis factor

Table 2. Therapeutic drug monitoring for anti-tumour necrosis factor (TNF) therapy

Clinical state	Trough level	Anti-drug antibody	Problem	Suggested action
Active disease	Low	Absent or low	Underdosing	Increase dose or reduce interval between doses
	Low	Present at high level	Loss of response as a result of anti-drug antibody	Switch within class to alternative anti-TNF
	Normal to high	Absent or low	Disease has become refractory to anti-TNF	Switch out of class
Remission	Low	Present at high level	Remission despite no drug present	Stop drug
	Normal	Absent or low	On target	Continue (or stop if clinically low risk)
	High	Absent or low	Supratherapeutic dose	Reduce dose or lengthen interval (or stop if clinically low risk)

> Real-world experience studies have demonstrated that vedolizumab is safe and effective for patients with inflammatory bowel disease

Vedolizumab

The α4β7 integrin is important for the recruitment of T-cells and monocytes through gut microvasculature into inflamed bowel tissue. Natalizumab, an antibody against α4β1- and α4β7-integrin, was the first anti-integrin monoclonal antibody to be used in the treatment of inflammatory bowel disease (Juillerat et al, 2013). However, antagonising α4β1-integrin reduces immune surveillance in the brain and is associated with the fatal reactivation of the John Cunningham (JC) virus which causes progressive multi-focal leukoencephalopathy. Vedolizumab is a humanized monoclonal antibody that specifically targets the α4β7 integrin thereby offering gut selectivity which reduces the risk of progressive multi-focal leukoencephalopathy.

The landmark registration trials, GEMINI I and II, proved the efficacy and safety of vedolizumab for use in moderate-to-severe ulcerative colitis and Crohn's disease respectively (Feagan et al, 2013; Sandborn et al, 2013). The GEMINI I trial showed that patients with ulcerative colitis given 300 mg intravenous vedolizumab induction therapy, at week 0 and 2, had higher clinical response rates than placebo at week 6 (47.7% *vs* 25.5%, $P<0.001$). Patients who had a response to vedolizumab at week 6 were then further randomized to receive vedolizumab either 8- or 4-weekly or to receive placebo. Clinical remission at week 52 was higher in the vedolizumab group compared to the placebo group (41.8%, 44.8% *vs* 15.9%, $P<0.001$). The similarly designed GEMINI II trial reported a modest but significantly higher clinical remission rate for patients given induction vedolizumab therapy compared to placebo (14.5% *vs* 6.8% respectively, $P=0.02$) but the clinical response rate was not significantly higher. This is likely a result of the transmural nature of Crohn's disease as well as a relatively slow induction effect of vedolizumab. However, at 52 weeks the trial reported significantly higher rates of clinical remission in the vedolizumab treatment arms compared to placebo (39% and 36.4% *vs* 21.6% placebo, $P<0.001$). GEMINI III assessed the efficacy of vedolizumab among patients with moderate-to-severe Crohn's disease and specifically focused on patients who had a previous anti-TNF failure (Sands et al, 2014). This trial reported no significant difference in rates of clinical remission between the patients treated with vedolizumab and placebo at 6 weeks. However, at 10 weeks there was a small but significant proportion of patients treated with vedolizumab in clinical remission (26.6% *vs* 12.1%, $P<0.001$).

Vedolizumab is administered via intravenous injection at a dose of 300 mg at week 0, 2, 6 and 8-weekly thereafter. Dose frequency can be increased if treatment response decreases and for patients with Crohn's disease an extra dose at 10 weeks can be administered if a suboptimal response is observed. Side effects include hypersensitivity, nasopharyngitis, headache, paraesthesia, infection, arthralgia and flu-like symptoms. Pooled data from several trials show that vedolizumab has a favourable safety profile with no increased risk of serious or opportunistic infections and a rate of malignancy which is similar to background risk in patients with inflammatory bowel disease (Colombel et al, 2017a). Importantly, there has been no reported incidence of progressive multi-focal leukoencephalopathy. Furthermore, several real-world experience studies have demonstrated that vedolizumab is safe and effective for patients with inflammatory bowel disease (Baumgart et al, 2016). Data from a group of eight English inflammatory bowel disease centres evaluating the clinical effectiveness and safety of vedolizumab (n= 203, 135 Crohn's disease and 68 ulcerative colitis patients) showed a higher rate of clinical remission in patients with ulcerative colitis *vs* Crohn's disease at week 52 of treatment (61.7% *vs* 41.2%, $P<0.0011$) which reflects results from the registration trials (Lenti et al, 2018).

While the evidence for vedolizumab is very compelling for its use in ulcerative colitis the effect in patients with Crohn's disease seems less strong and may take longer to evolve. In light of this National Institute for Health and Care Excellence recommends vedolizumab as potential first-line therapy for patients with ulcerative colitis but restricts use in Crohn's disease to those patients who have failed anti-TNF therapy. Future research directions for vedolizumab include identifying predictors of responders, the role of therapeutic drug monitoring, the role of concomitant immunosuppressants and its role in special situations such as pregnancy, extra-intestinal manifestations, peri-anal Crohn's and primary sclerosing cholangitis. There is some observational evidence that despite its gut-selective mode of action vedolizumab can improve extra-intestinal manifestations (Tadbiri et al, 2018) but conversely there have also been reports of de-novo development or worsening of previously diagnosed spondylarthropathies in patients receiving vedolizumab for their inflammatory bowel disease (Dubash et al, 2018).

Ustekinumab

The limited efficacy of current medical therapies available to patients with Crohn's disease led to the development of molecules that can block alternative inflammatory pathways. Ustekinumab is a fully human IgG1 monoclonal antibody to the p40 subunit of the pro-inflammatory cytokines IL-12 and IL-23. Blockage of the p40 protein prevents binding of IL-12 and IL-23 to their receptors on T-cells and NK cells which results in inhibition of Th1 and Th17 inflammatory responses.

The approval of ustekinumab for the treatment of moderate-to-severe Crohn's disease was based on three key

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studies: two induction trials (UNITI-1 and UNITI-2) and one maintenance trial (IM-UNITI) (Feagan et al, 2016). The UNITI-1 and UNITI-2 trials evaluated patients with moderate-to-severe Crohn's disease who were refractory to anti-TNF therapy (n=741) and conventional therapy (n=628) respectively. Patients were randomized in a 1:1:1 ratio to receive either induction with single dose 130 mg intravenous ustekinumab, weight-based intravenous ustekinumab (6 mg/kg) or intravenous placebo. Clinical response, defined as a decrease in Crohn's disease activity index score of ≥100 points or a Crohn's disease activity index score <150 points, was assessed at week 6 and was significantly higher in the ustekinumab groups in both trials (UNITI-1 34.3%, 33.7% and 21.5%, P<0.003; UNITI-2 51.7%, 55.5% and 28.7%, P<0.001). Patients who had a clinical response and completed the induction trials were then included in the maintenance trial, IM-UNITI (n=397). These patients were randomly assigned in a 1:1:1 ratio to receive either 90 mg ustekinumab subcutaneously every 8 weeks, 12 weeks or placebo. Clinical remission was higher in patients receiving ustekinumab subcutaneously *vs* placebo (8-weekly 53.1%, 12-weekly 48.8%, and placebo 35.9%, P<0.005 and P=0.04).

The National Institute for Health and Care Excellence has positioned ustekinumab for use in patients with moderate to severe Crohn's disease who have failed conventional therapy. Ustekinumab may be used before or after alternative biological therapies. Following a single intravenous induction with 6 mg/kg, 90 mg is given subcutaneously at week 8 followed by 8–12-weekly maintenance thereafter. Common side effects include headache, nasopharyngitis, pyrexia, headache, abdominal pain and infection. There are abundant long-term safety data for ustekinumab use in psoriasis (although differently dosed) showing no increased risk of infection, malignancy or demyelination compared to placebo (Papp et al, 2013).

There remains a debate where to place ustekinumab in treatment algorithms for inflammatory bowel disease. Given its efficacy for psoriasis it seems prudent to use it first line in patients with concomitant Crohn's disease and psoriasis and in those patients who paradoxically develop psoriasis on anti-TNF therapy. Moreover, as the drug has low immunogenicity it may have a role in patients with secondary loss of response to other biologic medication. Future research targets include its role in patients with ulcerative colitis and in special inflammatory bowel disease populations such as peri-anal Crohn's disease, paediatric inflammatory bowel disease, pregnancy and the elderly.

Choice of biological agent

The choice of different biological agents for first line or subsequent therapies depends on many factors. Mode of administration, infusion unit capacity and cost may influence decision making but disease phenotype, comorbidities and extra-intestinal manifestations are also important to consider. There is no ideal agent that is the best choice for every patient. Loss of response to therapy can be dealt with by dose adjustments, switch within or outside the class of biologics. Therapeutic drug monitoring can help decision making in this situation.

> **"A top-down approach using early intense immunosuppression instituted at diagnosis can be used for those patients with a poor prognosis."**

Treatment goals in inflammatory bowel disease

Traditionally, the therapeutic management of patients with inflammatory bowel disease was tailored to achieve and maintain clinical remission. However, symptoms are a poor surrogate marker for active inflammation and current treatment strategies seems to have little effect on altering the natural history of inflammatory bowel disease. Many patients with clinical remission have residual endoscopic mucosal inflammation, a marker associated with poor disease outcomes including increased rates of steroid administration, hospitalizations and colectomy (Colombel et al, 2010). Subsequently a shift in the treatment paradigm in inflammatory bowel disease with the focus on new objective therapeutic targets such as mucosal healing, radiological and biomarker targets has been proposed.

In addition to the classic step-up model of care, which involves intensifying immunosuppression along with disease severity, a top-down approach using early intense immunosuppression instituted at diagnosis can be used for those patients with a poor prognosis. The rationale for this approach originated from observations in rheumatoid arthritis that early biologic therapy reduced structural damage. There is growing evidence that early top-down treatment with combined anti-metabolite and biologic therapy is indicated for selected Crohn's disease patients with an unfavourable risk profile (*Table 3*)(Yarur et al, 2011). A study of 133 treatment-naïve Crohn's disease patients randomized to receive either early combined immunosuppression with anti-metabolite or anti-TNF

Table 3. Clinical predictors of poor disease outcomes in Crohn's disease

Younger age (<40 years) at diagnosis
Presence of perianal disease
Presence of stenotic disease
Involvement of the upper gastrointestinal tract
Requirement for corticosteroids during first flare-up
Absence of mucosal healing after induction of clinical remission
Smoking

From Yarur et al (2011)

KEY POINTS

- Biological therapy has become an integral part of the care of patients with inflammatory bowel disease.
- Anti-tumour necrosis factor biologics are often used as first-line biologic agents.
- The arrival of vedolizumab and ustekinumab provides new treatment choices especially for patients losing response to anti-tumour necrosis factor biologics.
- New treatment approaches include 'top down' and 'treat to target'.

(top-down) or conventional treatment (step up) showed that at 1 year, 61.5% of patients in the top-down group were in remission without corticosteroids or surgical resection compared with 42.2% in the step-up group (absolute difference 19.3%, 95% confidence interval 2.4–36.3%, P=0.028) (Khanna et al, 2015). In ulcerative colitis, early immunosuppression may reduce risk of dysplasia and help prevent disease extension but there is currently little evidence for a top-down approach.

More recently, a treat-to-target approach has been evaluated in patients with Crohn's disease. This involves frequent and repeated assessment of pre-defined targets, such as symptoms and biomarkers (faecal calprotectin and C-reactive protein), and intensifying therapy if the target is missed. The multi-centre CALM study randomized patients with early moderate to severe Crohn's disease into two treatment arms: a treat-to-target arm and a standard clinical management arm (Colombel et al, 2017b). Mucosal healing (a surrogate marker for better long-term outcomes) ulcerations was achieved more often in the treat-to-target arm (45.9% *vs* 30.3%, P=0.01). Furthermore, significantly more patients in the treat-to-target arm achieved steroid-free remission at 48 weeks (59.8% *vs* 39.3%, P<0.001). A treat-to-target approach to achieve mucosal healing in patients with ulcerative colitis has yet to be evaluated prospectively.

While waiting for results from long-term prospective trials which evaluate the validity of these approaches in altering disease course in inflammatory bowel disease the Selecting Therapeutic Targets in Inflammatory bowel disease (STRIDE) programme has developed recommendations for composite treatment targets of patient-reported outcomes and endoscopic mucosal remission in inflammatory bowel disease (Peyrin-Biroulet et al, 2015). Treat-to-target approaches and top-down approaches can be resource intensive and are often associated with higher direct health-care costs (Colombel et al, 2017b), but they have the potential to reduce overall costs by reducing the costs of adverse long-term health outcomes (e.g. hospitalization, surgery). While for the time being National Institute for Health and Care Excellence recommendations are being based on symptoms alone a shift towards treat-to-target and top-down approaches for select patients is to be expected.

When to discontinue biologic therapy remains controversial. National Institute for Health and Care Excellence guidance recommends that a clinical assessment is required every 12 months to decide whether to continue or stop therapy. Patients in 'deep remission' (free of symptoms and objective absence of inflammation) have a lower risk of flare after discontinuation of therapy. In the absence of deep remission flare rates can be as high as 80% at 1 year after stopping anti-TNF therapy. It is reasonable therefore to consider stopping therapy in patients meeting criteria for deep remission. However, in every case a benefit–risk assessment should be made involving the previous treatment history and personal circumstances. Patients who have failed several previous therapies or who are at risk of short bowel syndrome or other severe long-term complications will be better served with continuous therapy. There is no need to taper biologic therapy but step down to an immunomodulator where tolerated is a sensible approach.

Despite great improvements in the care of patients with inflammatory bowel disease with three different classes of biologics many patients fail to respond or suffer a loss of response to several classes of biologics. Unmet needs include therapies for those failing to respond to biological therapy in the first instance, better ways of overcoming loss of response, an improved understanding of the risks and benefits of combining biological agents from different classes and the development of more gut-selective therapies with a potential for less side effects. Fortunately there are many agents in development including biological therapies (anti-integrin etrolizumab, IL23p19 blocking agents) and novel small molecules including JAK and S1P inhibitors. The JAK inhibitor rofacitinib has received a license for use in patients with ulcerative colitis (Sandborn et al, 2017). With an increasing armamentarium of therapies the future of inflammatory bowel disease care is looking promising. **BJHM**

Conflict of interest: Dr CP Selinger has received unrestricted research grants from Abbvie, Janssen and Takeda, has provided consultancy to Dr Falk, Abbvie, Eli Lilly, Janssen and Takeda, and had speaker arrangements with Abbvie, Dr Falk, Janssen and Takeda; Dr I Carbery and Dr J Al-Asiry: none.

Baumgart DC, Bokemeyer B, Drabik A, Stallmach A, Schreiber S; Vedolizumab Germany Consortium. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice - a nationwide consecutive German cohort study. Aliment Pharmacol Ther. 2016 May;43(10):1090–1102. https://doi.org/10.1111/apt.13594

Colombel JF, Sandborn WJ, Rutgeerts P et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007 Jan;132(1):52–65. https://doi.org/10.1053/j.gastro.2006.11.041

Colombel JF, Sandborn WJ, Reinisch W et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr 15;362(15):1383–1395. https://doi.org/10.1056/NEJMoa0904492

Colombel JF, Sands BE, Rutgeerts P et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017a May;66(5):839–851. https://doi.org/10.1136/gutjnl-2015-311079

Colombel JF, Panaccione R, Bossuyt P et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2017b Dec;390(10114):2779–2789. https://doi.org/10.1016/S0140-6736(17)32641-7

Corte C, Saxena P, Tattersall S, Selinger C, Leong RW. When to use

biological agents in inflammatory bowel disease. J Gastroenterol Hepatol. 2012 Jul;27(7):1141–1149. https://doi.org/10.1111/j.1440-1746.2011.07056.x
Dubash S, Marianayagam T, Tinazzi I et al. Emergence of severe spondyloarthropathy-related entheseal pathology following successful vedolizumab therapy for inflammatory bowel disease. Rheumatology (Oxford). 2018 Sep 10. https://doi.org/10.1093/rheumatology/key267
Feagan BG, Rutgeerts P, Sands BE et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013 Aug 22;369(8):699–710. https://doi.org/10.1056/NEJMoa1215734
Feagan BG, Sandborn WJ, Gasink C et al; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016 Nov 17;375(20):1946–1960. https://doi.org/10.1056/NEJMoa1602773
Hanauer SB, Feagan BG, Lichtenstein GR et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002 May;359(9317):1541–1549. https://doi.org/10.1016/S0140-6736(02)08512-4
Hanauer SB, Sandborn WJ, Rutgeerts P et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006 Feb;130(2):323–333, quiz 591. https://doi.org/10.1053/j.gastro.2005.11.030
Juillerat P, Wasan SK, Fowler SA et al. Efficacy and safety of natalizumab in Crohn's disease patients treated at 6 Boston academic hospitals. Inflamm Bowel Dis. 2013 Oct;19(11):2457–2463. https://doi.org/10.1097/MIB.0b013e3182a32a0d
Khanna R, Bressler B, Levesque BG et al; REACT Study Investigators. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet. 2015 Nov;386(10006):1825–1834. https://doi.org/10.1016/S0140-6736(15)00068-9
Kim DH, Cheon JH. Pathogenesis of inflammatory bowel disease and recent advances in biologic therapies. Immune Netw. 2017;17(1):25–40. https://doi.org/10.4110/in.2017.17.1.25
Lenti MV, Levison S, Eliadou E et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study. Dig Liver Dis. 2018 Jul 18. pii: S1590-8658(18)30818-1. https://doi.org/10.1016/j.dld.2018.07.007
Molodecky NA, Soon IS, Rabi DM et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42; quiz e30. https://doi.org/10.1053/j.gastro.2011.10.001
Mowat C, Cole A, Windsor A et al; IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011 May 01;60(5):571–607. https://doi.org/10.1136/gut.2010.224154
Panaccione R, Ghosh S, Middleton S et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014 Feb;146(2):392-400.e3. https://doi.org/10.1053/j.gastro.2013.10.052
Papp KA, Griffiths CEM, Gordon K et al; PHOENIX 1 Investigators; PHOENIX 2 Investigators; ACCEPT Investigators. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol. 2013 Apr;168(4):844–854. https://doi.org/10.1111/bjd.12214
Peyrin-Biroulet L, Sandborn W, Sands BE et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015 Sep;110(9):1324–1338. https://doi.org/10.1038/ajg.2015.233
Ratnakumaran R, To N, Gracie DJ et al. Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. Scand J Gastroenterol. 2018 Jun 03;53(6):700–707. https://doi.org/10.1080/00365521.2018.1464203
Rutgeerts P, D'Haens G, Targan S et al. Efficacy and safety of retreatment with anti–tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology. 1999 Oct;117(4):761–769. https://doi.org/10.1016/S0016-5085(99)70332-X
Rutgeerts P, Sandborn WJ, Feagan BG et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 08;353(23):2462–2476. https://doi.org/10.1056/NEJMoa050516
Sandborn WJ, van Assche G, Reinisch W et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65.e1-3. https://doi.org/10.1053/j.gastro.2011.10.032
Sandborn WJ, Feagan BG, Rutgeerts P et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013 Aug 22;369(8):711–721. https://doi.org/10.1056/NEJMoa1215739
Sandborn WJ, Feagan BG, Marano C et al; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014 Jan;146(1):85-95; quiz e14-5. https://doi.org/10.1053/j.gastro.2013.05.048
Sandborn WJ, Su C, Sands BE et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017 May 04;376(18):1723–1736. https://doi.org/10.1056/NEJMoa1606910
Sands BE, Feagan BG, Rutgeerts P et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014 Sep;147(3):618-627.e3. https://doi.org/10.1053/j.gastro.2014.05.008
Selinger CP, Lenti MV, Clark T et al. Infliximab Therapeutic drug monitoring changes clinical decisions in a virtual biologics clinic for inflammatory bowel disease. Inflamm Bowel Dis. 2017 Dec;23(12):2083–2088. https://doi.org/10.1097/MIB.0000000000001258
Tadbiri S, Peyrin-Biroulet L, Serrero M et al; GETAID OBSERV-IBD study group. Impact of vedolizumab therapy on extra-intestinal manifestations in patients with inflammatory bowel disease: a multicentre cohort study nested in the OBSERV-IBD cohort. Aliment Pharmacol Ther. 2018 Feb;47(4):485–493. https://doi.org/10.1111/apt.14419
Yarur AJ, Strobel SG, Deshpande AR, Abreu MT. Predictors of aggressive inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2011 Oct;7(10):652–659.