Recent Advances in Gastroenterology

Edited by
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Chapter 1

Management of moderate-to-severe ulcerative colitis: 2024 update

Her Hsin Tsai

INTRODUCTION

The incidence and prevalence of inflammatory bowel disease (IBD) have been increasing globally, with the highest incidence in Europe and North America. Ulcerative colitis (UC) is the most common form of IBD, the annual incidence of about 5–20 per 100,000 person years, and prevalence of up to 500 cases per 100,000 in some parts of the world. UC affects a variable extent of the colon from the rectum extending proximally with primarily mucosal inflammation. Clinically, it presents as bloody diarrhoea, urgency, and abdominal pain, and runs a relapsing and remitting course. It is associated with significant morbidity, with an estimated 30–60% of patients experiencing at least one relapse per year, and approximately 20% of patients suffering from severe form of the disease. These symptoms have a major impact on sufferer's quality of life.

Treatment depends on severity and extent of the disease. The aim is to induce symptom-free remission of the disease and maintaining it. For mild-to-moderate disease, 5-aminosalicylate (orally and rectally) remains useful in both induction and maintenance therapy for UC. For moderate to severe disease, corticosteroids remain the primary therapy of UC but are limited by serious side effects. Should induction be successful, the steroids are withdrawn and replaced by immunosuppressants such as thiopurine analogues, e.g. azathioprine and 6-mercaptopurine.

More targeted therapies have been developed that specifically inhibit the mediators of gut inflammation. Infliximab is the first, an intravenously administered chimeric monoclonal antibody targeting tumour necrosis factor alpha (TNF-α), a key proinflammatory cytokine involved in gut inflammation. The ACT-1 trial showed that patients with moderate-to-severe UC had a clinical response rate to infliximab of 65.5% at week 8, and almost 50% maintained response at week 30 [1]. Adalimumab, a subcutaneously administered humanised anti-TNF antibody, was subsequently developed, with the ULTRA-2 trial demonstrating a clinical response rate of nearly 50% at week 8 [2]. These biologic therapies are well established and most physicians caring for these patients are comfortable with their use. They are also demonstrably cost effective, as prices have tumbled with the advent of generic biosimilars [3].

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In this chapter, we shall discuss recent advances in the treatment of moderate-to-severe UC. It is not meant to be a comprehensive discussion on the clinical management of UC. It will focus on evolving clinical concepts in the optimising of treatment and new and emerging drug therapy that will likely impact on the clinical management of UC either already licensed or likely to be in the very near future. The number of treatment choices are growing at a remarkable rate and is by understanding the mode of action of the drugs and trial data that the optimal choices can be made for the specific clinical problem.

OPTIMISING CONVENTIONAL THERAPIES

It is a common tendency to move onto a new treatment before optimising current and often cheaper or less toxic treatments. This may be due to pressures put onto the physician either from patient or carer or from pharmaceutical sales pitch. There are several questions the physician should ask before escalation of treatment. This is particularly true of IBDs.

1. **Are you treating the right disease?**
   It might seem an obvious question but there are a number of differential diagnoses that may ensnare the physician. The diagnosis is reached by a combination of clinical, radiological, endoscopic and histological features. This is why a multi-disciplinary approach is desirable, even essential if mistakes are to be not made.

2. **Has the severity and extent of ulcerative colitis been properly assessed?**
   It is a common mistake to equate subjective patient symptom reporting with disease activity. While all reported symptoms need to be addressed with a treatment plan, only mucosal inflammation will respond to immunological modulation. There is understandably often a large functional element in the patient's symptoms. Irritable bowel syndrome (IBS) often coexists with IBD and the physician will need to be cautious in equating symptoms with disease severity. Hence before escalation of treatment, the patient needs to be reassessed. The best tool is colonoscopy. It will demonstrate extent and severity of inflammation. A form of mucosal inflammation scoring should be adopted (e.g., Mayo score) and extent recorded. Biopsies may be helpful. If acute severe disease is suspected, it should be done cautiously and once it is clear that the disease is severe (Mayo 3), then the scope may be withdrawn, and a plain abdominal X-ray taken. This is not only safer but remarkably helpful in demonstrating extent of disease presence of mucosal thickening and serious complication of a dilated colon. CT scans (or MRI) can also be very helpful in the severe cases (See **Figures 1.1a** and **b**). In all non-urgent cases, colonoscopy is by far the most useful assessment tool.
   In recent years, faecal calprotectin has emerged as a useful tool in monitoring disease activity of UC. If done regularly, serial faecal calprotectin may be indicators of disease flare. However, the test is not reliable in predicting severity or extent of disease and should not be used as a justification for treatment escalation but should be used only as supporting evidence of mucosal inflammation [4].

3. **Is the disease acute severe?**
   Acute severe UC is a potentially life-threatening condition and patients are at risk for progressing to toxic megacolon (**Figure 1.1b**) or bowel perforation. Hence, recognition of this clinical condition is vital. In the original Truelove and Witts' [5] criteria it is characterised by:
   - Bloody stool frequency ≥ 6 per day

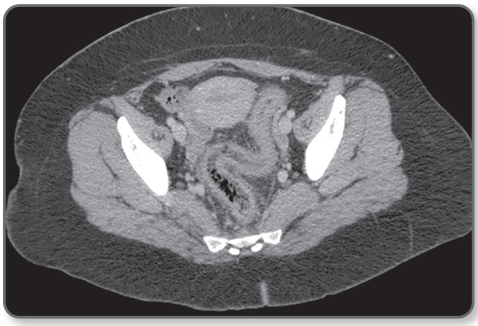


Figure 1.1a Sigmoid inflammation in patient with severe ulcerative colitis.

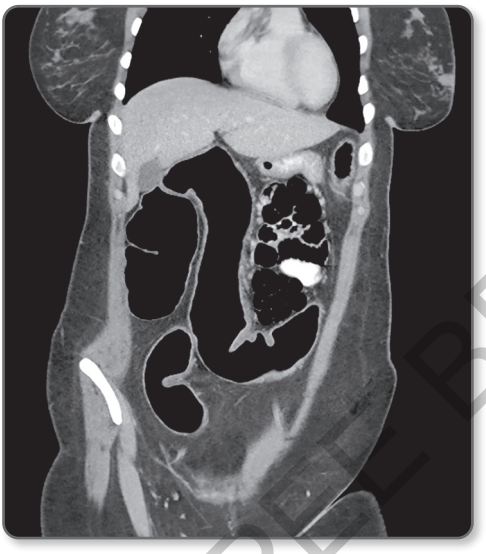


Figure 1.1b Colonic dilatation in acute severe ulcerative colitis (UC).

Plus at least one of the following types of evidence of systemic toxicity:

- Fever (temperature ≥ 37.8°C)
- Tachycardia (heart rate ≥ 90 beats/min)
- Anaemia (haemoglobin < 105 g/L)
- Elevated inflammatory marker [C-reactive protein (CRP) > 100 g/L, erythrocyte sedimentation rate]

A subgroup with abdominal distension and pain are described as acute fulminant colitis [5].

Patients with acute severe disease have a high risk of requiring colectomy and need to be recognised and admitted as an acute emergency and treated with fluids and intravenous steroids. They should be assessed frequently and if they do not respond within 3–5 days or if day 3 CRP remains very elevated, then they should be considered for treatment with cyclosporine or infliximab or surgery [6]. Comparative trials have shown no difference between cyclosporine and infliximab [7,8]. Furthermore, there is no evidence that medical therapy results in lower long-term colectomy rates, but it is generally accepted that elective surgery carries a lower morbidity [9,10].

4. **Have you optimised 5-ASA therapies?**
   5-ASA treatments are the mainstay in the management of mild-to-moderate UC. This is particularly true of distal disease like proctitis where the patient may experience a lot of urgency and frequency but may have very limited overall inflammatory load. Formal assessment may classify these patients are having moderate to severe disease even though the extent of inflammation may be very limited because of the dependence of scoring systems on bowel frequency counts. In this scenario, immunosuppression may not be the best treatment. Local treatment with 5-ASA products is often the key, with high-dose oral and rectal 5-ASA preparations having demonstrable efficacy. This approach is often underused [11].

5. **Have you optimised immunosuppressive therapies?**
   Immunosuppressive therapy, mainly the use of azathioprine (AZA) and 6-mercaptopurine (6MP), is the cornerstone of management of moderate-to-severe UC. Patience is required as the drug is slow acting, taking at least 3 months and sometimes up to 6 months to act. It may be used alongside 5-ASA or as monotherapy in patient's intolerant of 5-ASA. It should also be used with biologic therapy where it acts synergistically by suppressing antibody formation.

   These drugs have many toxic effects and as many as 25% of patients are intolerant of the drug but only 1–2% develop serious toxicity. Liver toxicity and myelosuppression are the principal severe adverse reactions. Thus, physicians may adopt a taciturn approach to the drug use for fear of toxicity and is a reason for suboptimal dosing in UC treatment. Enzyme testing and drug metabolite testing is helpful to optimise treatment.

   Thiopurine methyltransferase (TPMT) is the critical (**Figure 1.2**) enzyme in AZA and 6-MP metabolism and determines the levels of active molecule 6-thioguanine (6-TG) and toxic metabolite 6-methylmercaptopurine (6-MMP) levels. Approximately 89% of the population has wild type TPMT, which is associated with normal or 'high' TPMT enzyme activity, while 11% are heterozygous and have corresponding low TPMT enzyme activity. A small number (1 in 300) of the population are homozygous for mutations of TPMT and thus have negligible activity, which causes 6-MP to be preferentially metabolised to produce high levels of 6-TG, which then leads to bone marrow suppression. Very high levels of TPMT may result in increased accumulation of 6-MMP increasing risk of liver toxicity. Thus, determining the activity of TPMT may help to optimise treatment.

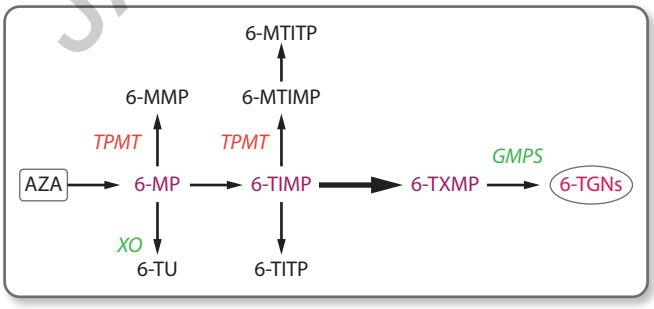


Figure 1.2 Azathioprine metabolism: Azathioprine is serially converted to 6-TGNs and metabolised in a rate-limiting fashion into 6-MMP by TPMT (thiopurine methyltransferase) enzyme. AZA, azathioprine; GMPS, guanosine monophosphate synthetase; MMP, methylmercaptopurine; MTIMP, methylthioinosine monophosphate; TG, thioguanine; TGN, thioguanine nucleotide; TIMP, thioinosine monophosphate; TITP, thioinosine triphosphate; TU, thiourea acid; XO, xanthine oxidase.

Direct measurements of drug metabolite levels are available. Levels of 6-MMP can also be helpful to predict liver toxicity. The active moiety 6-TG can be a good measure of optimal dose of the drug. A recent meta-analysis of studies looking at 6-TG levels also demonstrated that clinical remission was significantly more likely among patients with 6-TG levels over a cut-off value between 230 and 260 pmol/8 × 108 red blood cells (odds ratio 3.2, 95% CI 2.4–4.1) [12].

Optimising anti-tumour necrosis factor treatments

When it is clear that in the patient who has failed or is intolerant of the conventional treatments for UC, and that the patient has disease of at least moderate in severity, then a biological drug is the next step. It is usual to choose an anti-TNF as it is well established and availability of biosimilars have made it more affordable. There are some recent evolving concepts that may help to optimise therapy.

Addition of immunosuppressive agents to anti-tumour necrosis factor treatment improves efficacy

In a clinical trial of infliximab monotherapy versus infliximab plus azathioprine versus azathioprine alone (UC-SUCCESS), corticosteroid-free remission at week 16 was achieved by 39.7% of patients receiving infliximab/azathioprine, compared with 22.1% receiving infliximab alone ($p = 0.017$) and 23.7% receiving azathioprine alone ($p = 0.032$) [13]. The effect is likely to be due to improved infliximab serum concentrations due to reduced antibody development in patients on combination therapy. Sub-analyses of a similar Crohn's study (SONIC) showing higher week 30 infliximab trough levels with combination versus infliximab monotherapy, 3.5 μg/mL versus 1.6 μg/mL ($p < 0.001$), and lower incidence of anti-infliximab antibody, 0.9% versus 14.6%. Interestingly, serious adverse events were actually lower with combination versus infliximab monotherapy (15.1% vs. 23.9%, $p = 0.04$) [14].

The dose and length of azathioprine treatment required remains uncertain, but antibody suppression requires only a small dose of azathioprine hence it is sensible to keep the patient on azathioprine for at least 3 months.

Treatment goals and targets

It has been noted in many trials involving infliximab that patients who had achieved mucosal healing had a more durable remission than those with symptom resolution without complete mucosal healing [15]. In 2015, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee defined the treat-to-target approach for IBD, which shifted the goal of UC treatment from short-term symptom resolution to long-term prevention of disease complications (dysplasia/cancer, hospitalisations and colectomy) [16]. The three most promising composite targets for UC were symptom resolution (normalisation of bowel habit and absence of rectal bleeding), endoscopic mucosal healing (Mayo or UCIES inflammation score of 0) and faecal calprotectin < 100 μg/g. Although this area is still subject to ongoing long-term clinical investigation, early indication is that target achievement with aggressive medical therapy is associated with better outcome, lower colectomy rates and hospitalisations [17].

Personalising treatment

The ultimate refinement in the management of UC is to accurately personalise treatments for the individual patient. This depends on the ability of the clinician to accurately predict the likely clinical course and prognosis of the disease. This can be difficult to achieve. Currently, we depend on clinical features, endoscopic appearance and response to therapy to help us to predict those who are likely to relapse or end up with colectomies. These measures are not adequate. Genetic studies have not been very helpful. Current best practice of personalising treatment is based on optimising treatments and selecting the right targets as already discussed above. The future may be the identification of biomarkers that can accurately predict the patients who are likely to have more aggressive disease. One concept is to identify T-cell transcriptional signatures or histological characteristics and using artificial intelligence as a tool to identify and predict disease outcomes and select the best therapeutic pathway for the individual patient [18,19].

Prospective and scheduled therapeutic drug monitoring

Therapeutic drug monitoring is now widely available both for thiopurines and anti-TNFs. With anti-TNFs both trough drug levels taken just before a scheduled dose and antibody levels are available. Currently, the majority of clinicians perform trough and antibody levels reactively in response to suboptimal treatment response. Prospective scheduled monitoring is regarded as expensive but with costs of therapeutic drug monitoring falling due to the economies of scale, scheduled testing may become increasingly the norm. There is no doubt that it improves patient outcome and gastroenterological associations are recommending its more widespread use [20]. Recent studies suggest that prospective therapeutic drug monitoring may also be highly cost-effective [21].

NEW DRUGS

Although anti-TNFs have revolutionised treatment of UC, some 40–60% still fail to respond. If the patient initially responded but then lose response (secondary failure to respond) or if antibody formation is identified as the reason for failure, then switching to a different drug within this class may be appropriate. But, when the patient never responded to anti-TNFs (primary failure to respond) or when anti-TNFs have been optimised by scheduled therapeutic drug monitoring and patient still has inadequate response to therapy then a change in class of drug is indicated. Fortunately, there are several such drugs to choose from, many already licensed and others in various stages of development and certification. These new drugs fall into four classes (see **Figure 1.3**):

1. Anti-adhesins
2. Anti-interleukin (IL)-12 and IL-23
3. Janus kinase (JAK) inhibitors
4. Sphingosine 1-phosphate receptor (SP1R) agonists

Anti-adhesion agents

One of the key components of the inflammatory response is the ability of the body's immune system to recruit immune modulator cells to the part of the body where they are needed. This is through trafficking of inflammatory cells via the circulatory system. To facilitate this the vascular endothelium of vessels neighbouring the areas where inflammatory cells are required to express on its surface the mucosal addressin-cell

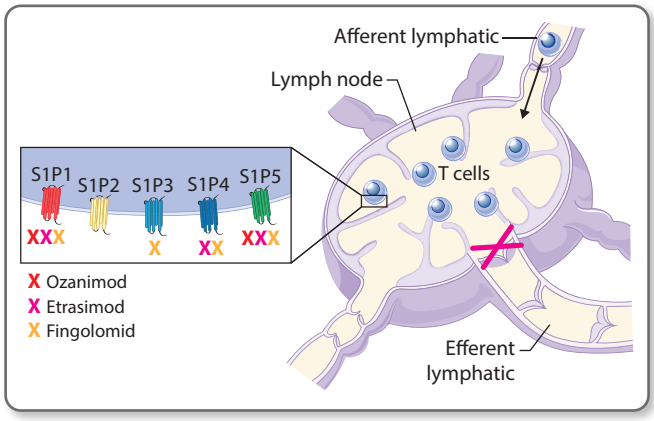
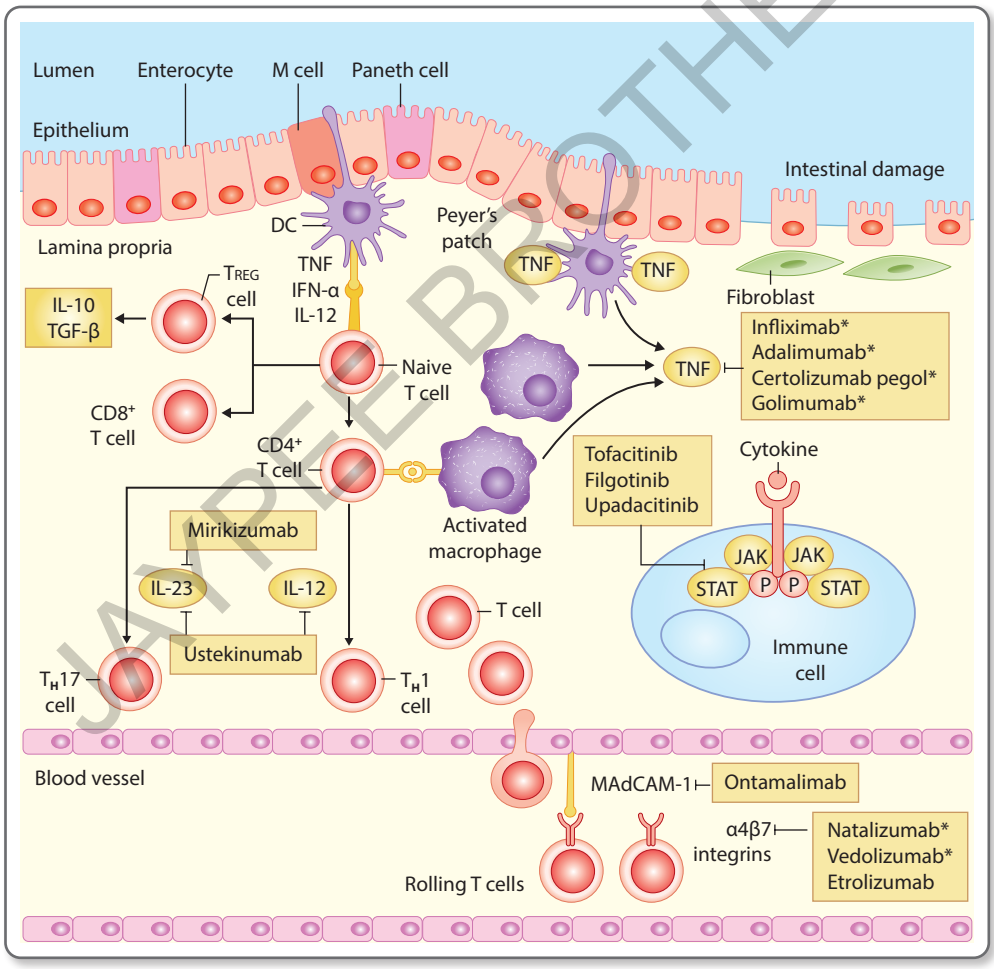


Figure 1.3 Immune targets of ulcerative colitis (UC). With permission from Danese et al. 2015 [22] and Shukla and Sands [23]



adhesion molecule (usually abbreviated, MadCAM-1) which binds to integrins expressed on circulatory T-cells (**Figure 1.3**). These integrins are heterodimeric receptors composed of an α- and β-subunit, that is expressed on the surface of circulating lymphocytes when they are activated. This process leads to the binding of circulating lymphocytes onto the endothelium and migration into the lamina propria and tissue, contributing to the inflammatory process in IBD [24].

These integrins and MAdCAM-1 are thus potential therapeutic targets for IBD therapy. Integrin antagonists are a class of monoclonal antibodies that can block the trafficking of lymphocytes to the intestinal endothelium. The first integrin antagonist to emerge is natalizumab, a humanised immunoglobulin (IgG)-4 monoclonal antibody that leads to inhibition of the α-4 integrin. Unfortunately, the use of natalizumab was limited by associated increased incidence of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease of the central nervous system caused by the opportunistic human John Cunningham (JC) virus. Vedolizumab (also known as LDP-02 and MLN02, MLN002), a humanised monoclonal IgG1 antibody, was subsequently developed as a gut selective anti-integrin specifically targeting α4β7 integrins in the gut and importantly not the integrins found in the CNS [24,25].

The efficacy of vedolizumab was demonstrated in two integrated regulatory trials (GEMINI 1). Response rates at week 6 were found to be 47.1% and 25.5% among patients in the vedolizumab group and placebo group respectively [95% confidence interval (CI) 11.6–31.7; $p < 0.001$]. At week 52, 41.8% of patients who continued to receive vedolizumab every 8 weeks were in clinical remission (Mayo Clinic score ≤ 2 and no subscore > 1), as compared with 15.9% of patients who switched to placebo (95% CI 14.9–37.2; $p < 0.001$) [26,27].

There may be advantages of using vedolizumab as a second-line biologic therapy in UC. Its mode of action is very different from anti-TNF and represents a change in class. In theory, changing of one anti-TNF to another would only be effective if there is drug tolerance due to antibody formation. Primary infliximab failures, that is those who have never responded to anti-TNF are not likely to respond to another anti-TNF. The mode of action of vedolizumab also appears more benign compared to anti-TNFs as it does not interfere with critical antibacterial, especially antimycobacterial pathways which makes anti-TNFs so hazardous in TB positive individuals. In this respect, there are compelling reasons to suggest that vedolizumab is less harmful than anti-TNFs [28].

Treatment is given as an intravenous (IV) infusion with an induction of 300 mg at weeks 0, 2 and 6 followed by 8 weekly dosing of 300 mg. There are indications from studies that vedolizumab may take longer than anti-TNFs to achieve therapeutic results. Clinical response may not be apparent until week 10 and hence a little patience from the clinician and forewarning to the patient would be judicious. Some would advocate an additional dose at week 10 if there is a lack of adequate response at week 8.

Using vedolizumab as a first-line biologic therapy also can be considered. At present the cost differential to generic infliximab is too high to make it is a cost-effective strategy. This is based on equal efficacy of both biologic treatments. However, recent data may suggest otherwise. A network meta-analysis has suggested that vedolizumab is superior to adlimumab [29]. This finding is now confirmed by a head-to-head study between adalimumab and vedolizumab. In a randomised trial comparing vedolizumab with adalimumab in over 700 patients with moderately to severely active UC, vedolizumab resulted in a significantly higher rate of clinical remission (31% vs. 22%) [30]. The rate of serious infections was similar in both groups (<2%). The therapeutic gain may well be sufficiently large to make vedolizumab a cost-effective first-line

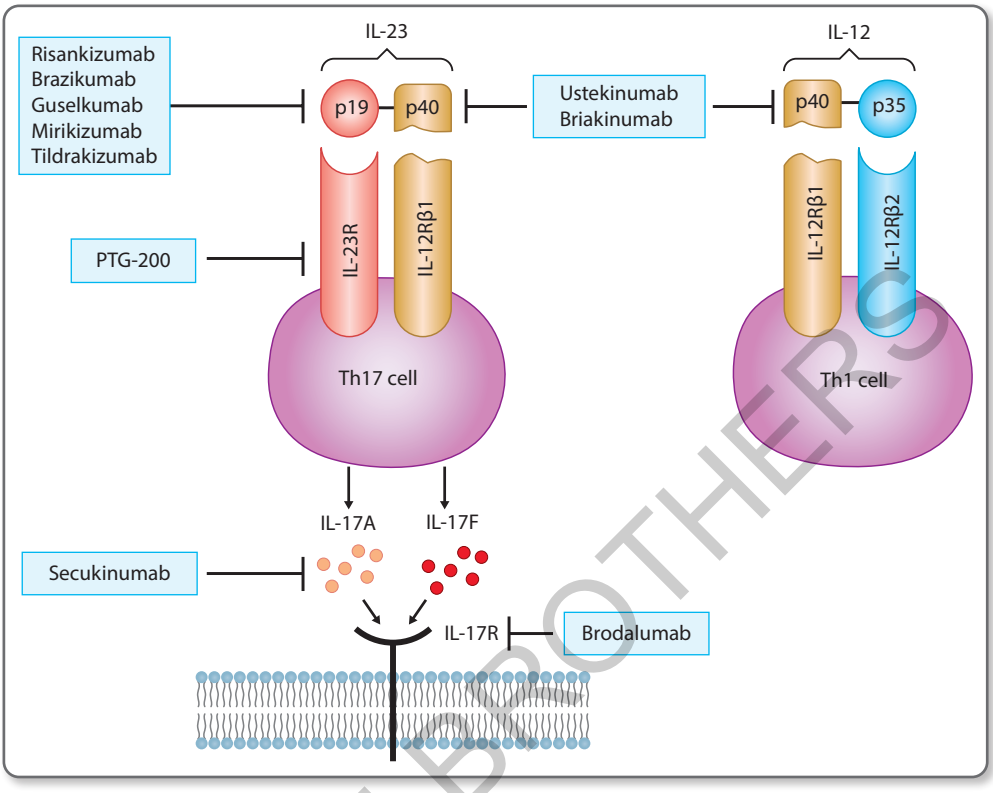


Figure 1.4 Interleukin (IL)-12 and IL-23 antibodies. With permission from Schmitt et al [36].

therapy for UC. A recent network meta-analysis suggests vedolizumab may well have the best safety record of the new agents [31].

Etrolizumab is very similar, being a humanised monoclonal antibody against specifically at the β7 subunit of integrins α4β7 and αEβ7. Studies on the induction and maintenance treatment of UC are very promising [32,33]. A study of etrolizumab in anti-TNF failures showed more modest, but not sustained response [34].

An antibody to the adhesion MadCAM-1, ontamalimab, is also under development [35].

Anti-interleukin antibodies

The proinflammatory cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23) play an important role in the pathophysiology of Crohn's disease and UC [37]. They are produced mainly by macrophages and antigen-presenting cells (APCs) after antigenic stimulation. These cytokines bind to receptors of $CD4^+$ T cells and lead to their differentiation into activated Th1 and Th-17 cells (see **Figure 1.4**). Thus, IL-23 appears to play a significant role as a mediator of intestinal inflammation and tissue damage. The IL-23/Th-17 axis may be the critical driver of this chronic inflammation. Thus, it is a legitimate therapeutic target [38]. Furthermore, the IL-23 receptor mutations have been identified as a possible *IBD* gene [39]. Ustekinumab, a fully humanised immunoglobulin G1 kappa monoclonal antibody that binds with high affinity to the p40 subunit found in both the human IL-12 and IL-23.

It has recently been approved for the treatment of moderately to severely active UC in adults. Ustekinumab prevents IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface receptor protein IL-12Rβ1. Through this mechanism of action, ustekinumab effectively neutralises both IL-12 (Th-1)- and IL-23 (Th-17)-mediated cellular responses. Mirikizumab, risankizumab and brazikumab all target specifically the p19 fraction which thus targets IL-12 only. Thus, it more specifically targets Th-17 responses and as they are the predominant inflammatory response in UC, it is a logical and more specific target.

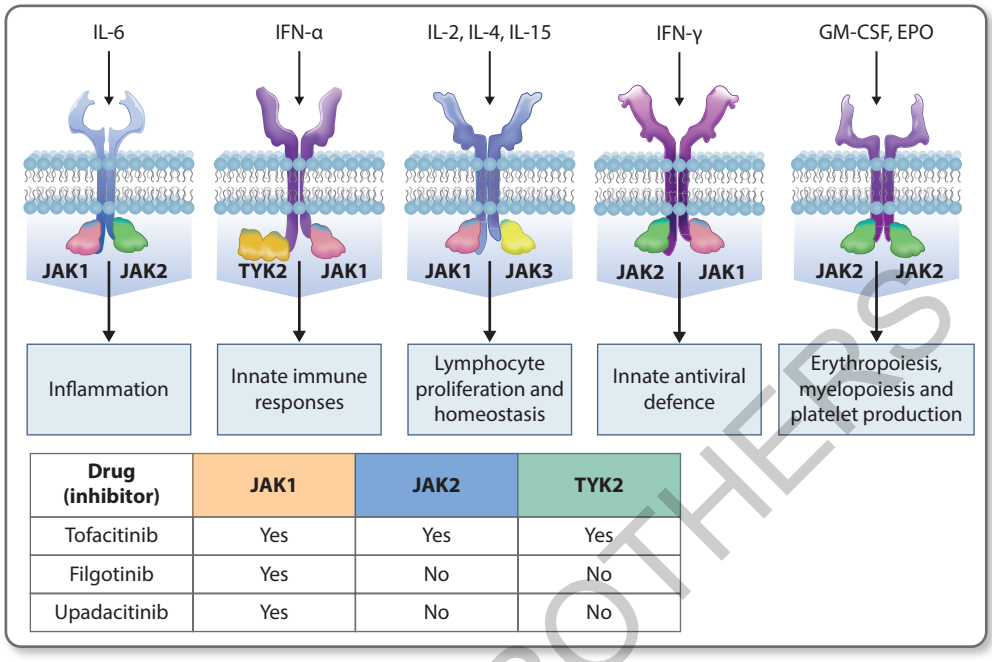
Evidence for the efficacy of ustekinumab in UC had been investigated and encouraging results published recently [40]. In this study, the percentage of patients who had clinical remission at week 8 among patients who received intravenous ustekinumab at a dose of 130 mg (15.6%) or 6 mg/kg (15.5%) was significantly higher than that among patients who received placebo (5.3%) ($p < 0.001$ for both comparisons). Among patients who had a response to induction therapy with ustekinumab and underwent a second randomisation, the percentage of patients who had clinical remission at week 44 was significantly higher among patients assigned to 90 mg of subcutaneous ustekinumab every 12 weeks (38.4%) or every 8 weeks (43.8%) than among those assigned to placebo (24.0%) ($p = 0.002$ and $p < 0.001$, respectively). The incidence of serious adverse events with ustekinumab was similar to that with placebo. However, there were two deaths (one each from acute respiratory distress syndrome and haemorrhage from oesophageal varices) and seven cases of cancer (one each of prostate, colon, renal papillary, and rectal cancer and three nonmelanoma skin cancers) among 825 patients who received ustekinumab and no deaths and one case of cancer (testicular cancer) among 319 patients who received placebo. Although these do not constitute a clear hazard signal, some caution must be taken until more data becomes available. The National Institute for Health and Care Excellence (NICE) guidance has been published [41].

Mirikizumab regulatory trials LUCENT-1 and 2 have recently been published in full. A total of 1,281 patients underwent randomisation in the induction trial, and 544 patients with a response to mirikizumab underwent randomisation again in the maintenance trial. Significantly higher percentages of patients in the mirikizumab group than in the placebo group had clinical remission at week 12 of the induction trial (24.2% vs. 13.3%, $p < 0.001$) and at week 40 of the maintenance trial (49.9% vs. 25.1%, $p < 0.001$) [42]. It too has seen the Food and Drug Administration (FDA) approval and the NICE technology appraisal published in the United Kingdom [43].

Risankizumab, another IL-23 antibody, is currently being assessed in UC after encouraging results in CD [44] (Clinical Trial No. NCT03398135).

Janus kinase/signal transducer and activator of transcription pathway inhibitors

Cytokines are released by the immune system in response to a signal principally by gut stellate cells or macrophages. They bind to specific receptors on the T cell, triggering activation and synthesis of specific proteins that initiate the immune response. Cytokines can take the form of many structurally unrelated proteins that are typed according to their binding to distinct receptor families, which include type I cytokine receptors, type II cytokine receptors, the TNF receptor family and the IL-1 receptor family receptors. The cytokines bind to the relevant receptor and trigger intracellular changes, resulting in signal transduction and trigger gene expression. The signal transduction is via various protein kinases. The Janus kinase (JAK) is a family of receptor-associated tyrosine



Drug (inhibitor)	JAK1	JAK2	TYK2
Tofacitinib	Yes	Yes	Yes
Filgotinib	Yes	No	No
Upadacitinib	Yes	No	No

Figure 1.5 The Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway and its inhibitors.

Source: Parigi et al [45] and Traves et al [46].

kinases that are essential for the cytokine signalling cascade (**Figure 1.5**), downstream of type I and type II cytokine receptors [47]. The JAK-*s*ignal *t*ransducers and *a*ctivators of *t*ranscription (STAT) pathway plays an important role in innate immunity, adaptive immunity, and haematopoiesis, participating in cellular processes such as cell growth, survival, differentiation, and migration. There are four members of the JAK family (JAK1, JAK2, JAK3, and TYK2) and seven signal transducers and transcription activators called signal transducer and activator of transcription, or STAT (STAT 1–4, 5a, 5b and 6). The unique structure of each JAK clearly distinguishes them from other members of the protein tyrosine kinase family [48].

Ulcerative colitis and Crohn's disease involve many cytokines signalling which in turn depend on JAK-STAT pathway for immune cell gene transcription. The key cytokines in the pathogenesis of IBD belong to type I and type II cytokines receptors. These are the receptors of certain key cytokines namely IL-6, IL-5, IL-9, IL-10, IL-13, IL-12/23, IL-22, granulocyte–macrophage colony-stimulating factor (GM-CSF) and IFN-γ. These cytokines all signal through the JAK/STAT pathway. In contrast, the cytokines TNF, IL-1 and IL-17, which are the other major drivers of IBD, do not use the JAK-STAT pathway in their signalling pathways but they do, however, induce the expression of a wide range of downstream proinflammatory cytokines, that in turn depend on JAK/STAT signalling [49].

Thus, specific inhibitors of these kinases are a logical target as a treatment of inflammatory conditions. Several of these molecules are in development and are small, orally active molecules. To date, three agents have been brought to the market. Tofacitinib was the first JAK inhibitor approved for the treatment of moderate-to-severely active UC by the FDA (US) and the European Medicines Agencies (EMA) (Europe) and appraised by the

NICE (UK) [50–52]. This was swiftly followed by filgotinib and upadacitinib. They do differ in their specificity of their JAK inhibitor activity. Tofacitinib (Xeljanz, Pfizer) is a pan-JAK inhibitor, that preferentially inhibits JAK1, JAK3 and TYK2, in a dose-dependent fashion. Oral tofacitinib is well absorbed and is cleared principally by the liver. It has a short half-life of 3 hours [53].

Tofacitinib was found to be effective for induction of remission for patients with UC. In two randomised trials (OCTAVE induction 1 and 2 trials of 598 and 541 patients, respectively), patients with moderate-to-severe UC who received tofacitinib 10 mg twice daily experienced remission at 8 weeks more frequently compared with those receiving placebo; for OCTAVE 1, 18% vs. 8% (absolute difference 10, 95% CI 4–16) and for OCTAVE 2: 17% vs. 4% (absolute difference 13, 95% CI 8–18) [54]. In the OCTAVE Sustain trial, 593 patients who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. The primary end-point was remission at 52 weeks which occurred in 34.3% of the patients in the 5-mg tofacitinib group and 40.6% in the 10-mg tofacitinib group versus 11.1% in the placebo group ($p < 0.001$ for both comparisons with placebo) [54].

The onset of action of tofacitinib varies greatly with some patients responding rapidly, while for other patients, response may take up to 8 weeks. Caution should be used when prescribing tofacitinib for patients with a history of thromboembolic disease, cardiovascular disease, or those ≥50 years old with at least one cardiovascular risk factor because of an increased risk of thromboembolic events and mortality in patients who were treated with tofacitinib.

Filgotinib and upadacitinib have been developed as more selective JAK inhibitors, being more highly specific in blocking JAK1 compared to tofacitinib.

Janus kinase inhibition by filgotinib and upadacitinib showed promise in early clinical trials in moderate-to-severe UC. The pivotal regulatory trial data for filgotinib and upadacitinib has been published in full recently in the Lancet in 2021 [55] and 2022 [56], respectively. NICE appraisal fairly quickly followed and guidance has been published [50–52].

The filgotinib trial involved two study groups with two dose regimens. At week 10, a greater proportion of patients given filgotinib 200 mg had clinical remission than those given placebo (induction study A 26.1% vs. 15.3%, difference 10.8%; 95% CI 2.1–19-5, $p = 0.0157$; induction study B 11.5% vs. 4.2%, 7.2%; 1.6–12.8, $p = 0.0103$). At week 58, 37.2% of patients given filgotinib 200 mg had clinical remission versus 11.2% in the respective placebo group (difference 26.0%, 95% CI 16.0–35.9; $p < 0.0001$). The studies involving filgotinib 100 mg was less convincing [55].

Turning to upadacitinib, the main trial involved two induction groups UC1 and UC2 with 472 and 552 patients, respectively (U-ACHIEVE and U-ACCOMPLISH). Statistically and significantly more patients achieved clinical remission with upadacitinib 45 mg [83 (26%) of 319 patients in UC1 and 114 (34%) of 341 patients in UC2] than in the placebo group [seven (5%) of 154 patients in UC1 and seven (4%) of 174 patients; $p < 0.0001$; adjusted treatment difference 21.6% (95% CI 15.8–27.4) for UC1 and 29.0% (23.2–34.7) for UC2]. In the maintenance study (UC), clinical remission was achieved by statistically significantly more patients receiving upadacitinib [15 mg 63 (42%) of 148; 30 mg 80 (52%) of 154] than those receiving placebo [18 (12%) of 149; $p < 0.0001$; adjusted treatment difference 30.7% (21.7–39.8) for upadacitinib 15 mg versus placebo and 39.0% (29.7–48.2) for upadacitinib 30 mg vs. placebo] [56].

In terms of safety profile of JAK inhibitors, it appears to be similar to other immunosuppressive drugs with exception of infections particular herpes zoster infection

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