

# Ulcerative colitis: an update

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## ABSTRACT

**Ulcerative colitis is a relapsing and remitting disease that is increasing in incidence and prevalence. Management aims to achieve rapid resolution of symptoms, mucosal healing and improvement in a patient's quality of life. 5-aminosalicylate acid medications remain the first-line treatment for mild to moderate disease. In the event of suboptimal response to these medications, escalation to immunosuppressive medications and biologics may be necessary. Importantly, despite best medical therapy, surgery may be required in a proportion of patients. The future will likely see an array of new therapeutic options for those with ulcerative colitis with the potential for a more personalised treatment approach.**

## Introduction

Ulcerative colitis (UC) is a relapsing and remitting inflammatory bowel disease (IBD) characterised by mucosal inflammation which starts distally and can extend proximally to involve the whole colon. It has a reported incidence in the UK of 12.6/100,000 person years (95% confidence interval (CI) 11.4–13.9).<sup>1</sup> Importantly, prevalence appears to be rising with the most recent data from the Lothian region highlighting a point prevalence of 432/100,000.<sup>2</sup> UC has a bimodal age distribution with an incidence peak in the second or third decades and a second peak between 50 and 80 years. The aetiology involves interactions between the environment, immune system, gut microbiome and a genetic predisposition to disease.<sup>3</sup> Ulcerative colitis presents with bloody diarrhoea, frequency, abdominal pain, fatigue and faecal incontinence.

The Montreal classification groups UC patients, based on their maximal disease extent, into E1 or proctitis (disease limited to the rectum); E2 or left-sided disease (distal to splenic flexure); and E3 or extensive colitis (disease extends proximal to splenic flexure).<sup>4</sup> Patients with left-sided disease or extensive colitis are associated with higher risks of medication usage, colectomy and colorectal cancer.<sup>4</sup> Besides disease extent, the main risk factors for colorectal dysplasia/cancer in UC include disease duration; active endoscopic or histological inflammation; presence of a stricture or post-inflammatory polyps; family history of colorectal cancer; and associated primary sclerosing cholangitis (a chronic inflammatory bile duct disorder which affects 3–7% of UC patients).<sup>5</sup> Other extra-intestinal manifestations of UC include,

in order of frequency, anaemia, arthropathy (axial or peripheral), cutaneous (erythema nodosum or pyoderma gangrenosum) and ocular manifestations (anterior uveitis or episcleritis), most of which mirror UC disease activity, except for ankylosing spondylitis and peripheral polyarthritis (Table 1).<sup>4</sup>

## Therapeutic goals and targets

In 2015, the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative made recommendations about

## Key points

Ulcerative colitis is common, and incidence and prevalence are increasing.

Goals of treatment are to achieve prompt symptom amelioration and heal disease at the mucosal level, while restoring overall quality of life for the patient.

Patient engagement in their care and monitoring (with symptoms in addition to objective markers of inflammation) are key to optimal management so that therapies can be escalated as necessary.

5-ASA drugs represent the main therapies for mild to moderately active UC, and optimising adherence is important.

In UC patients with inadequate response to 5-ASA, immunosuppressive or biologic therapies are indicated, and choice is dependent on multiple factors, including patient choice.

Surgical options for ulcerative colitis are important to discuss with patients and include restorative options such as an ileoanal pouch or, rarely, an ileorectal anastomosis or a permanent ileostomy.

The future will see an array of new treatments with head-to-head trials allowing us to position treatments correctly.

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**Table 1. Investigations for ulcerative colitis**

Investigation	Type of investigation	Common findings in UC	Notes
Blood tests	Full blood count Urea and electrolytes C-reactive protein Vitamin D and bone profile Haematinics Liver biochemistry	Anaemia, thrombocytosis, low vitamin D and raised inflammatory markers	Consider pre-immunosuppressant/biologic screen in those likely to need escalation to immunosuppressant/biologic therapy (including TPMT, viral serology, quantiferon) Primary sclerosing cholangitis can be associated with UC and can present with deranged liver biochemistry
Stool cultures	<i>Clostridioides difficile</i> toxin assay MC&S	Should be negative if UC, but infections such as <i>C difficile</i> can co-exist	Take a thorough history, including travel history to rule out other causes Recent antibiotic use may be associated with <i>C difficile</i>
Faecal calprotectin	Indicates migration of neutrophils to the lumen via the intestinal mucosa	A level of 50–100 µg/g has a high negative predictive value of 98–99% in the diagnosis of IBD	Can be used as a method of monitoring treatment response
Endoscopy	In acute setting, flexible sigmoidoscopy Ileocolonoscopy is recommended in all patients to delineate disease extent, severity of inflammation and to exclude Crohn's disease; also for surveillance	Erythema, oedema, loss of vascular pattern, blood and ulcers/erosions	Mayo score and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score are used to assess severity of ulcerative colitis endoscopically
Histology	Recommend at least two biopsies from each bowel segment for histological assessment	No histological features are diagnostic of UC, but basal plasmacytosis, crypt atrophy/distortion and villous surface irregularity are suggestive of UC	The presence of granulomas is more suggestive of Crohn's disease
Imaging	Abdominal X-ray	Thumbprinting, lead-piping, oedema and toxic megacolon	
Imaging	Cross sectional imaging: CT/MRI	Bowel wall oedema and inflammatory pseudopolyps	Small bowel imaging can help differentiate between UC and Crohn's disease in challenging cases

CT = computed tomography; IBD = irritable bowel disease; MC&S = microscopy, culture and sensitivity; MRI = magnetic resonance imaging; TPMT = thiopurine methyltransferase; UC = ulcerative colitis.

therapeutic targets in IBD which were later updated in December 2020 in the SPIRIT consensus.<sup>6,7</sup> In summary, this consensus agreed that UC treatment goals should address a composite of clinical and endoscopic outcomes (potentially with use of surrogate measures of inflammation, such as faecal calprotectin), in addition to the ultimate goals of addressing impact on a patient's life (health-related quality of life, disability and faecal incontinence), preventing disease extension, surgery, permanent stoma, and dysplasia or cancer.

### Determining severity of disease presentation

Disease severity is measured by assessment of clinical and biochemical parameters, as showcased by the modified Truelove and Witts criteria (Table 2).<sup>4</sup> Endoscopically, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is the

only validated scoring system to assess severity, however, the Mayo score is commonly used in clinical practice due to its simplicity in application.<sup>4,8</sup>

### Medical therapy

5-aminosalicylic acid (5-ASA) drugs represent the standard therapy for patients with mild to moderate disease activity for induction and maintenance of UC. In patients with mild to moderate UC proctitis, 5-ASA suppositories are considered the first-line therapy, more so than oral 5-ASA monotherapy and rectal corticosteroids.<sup>4</sup> In case of suboptimal response, addition of oral 5-ASA therapy should be the next step.<sup>4</sup> If response remains incomplete, adding a corticosteroid suppository and/or optimising the oral 5-ASA dosing is recommended.<sup>4</sup> UC patients with left-sided disease or extensive colitis should be offered dual therapy with oral 5-ASAs and topical

**Table 2. Modified Truelove and Witts criteria**

Parameter	Mild	Moderate	Severe
Bloody stool per day, n	<4	4–6	>6
Pulse, beats per minute	<90	≤90	>90
Temperature, °C	<37.5	37.5–37.8	>37.8
Haemoglobin, g/dL	>11.5	11.5–10.5	<10.5
ESR, mm/h (or CRP, mg/L)	<20 (normal)	20–30 (<30)	>30 (>30)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

5-ASA.<sup>4</sup> Oral 5-ASA doses of 2–3 g daily are sufficient in the induction of remission of most UC patients with mild to moderate activity.<sup>4</sup> However, higher dosage ( $\geq 4$  g daily) has been proven more effective in achieving clinical remission.<sup>4</sup> 5-ASAs are well tolerated; renal impairment is a rare and an unpredictable adverse event, hence renal function should be checked regularly after 5-ASA initiation.<sup>4</sup>

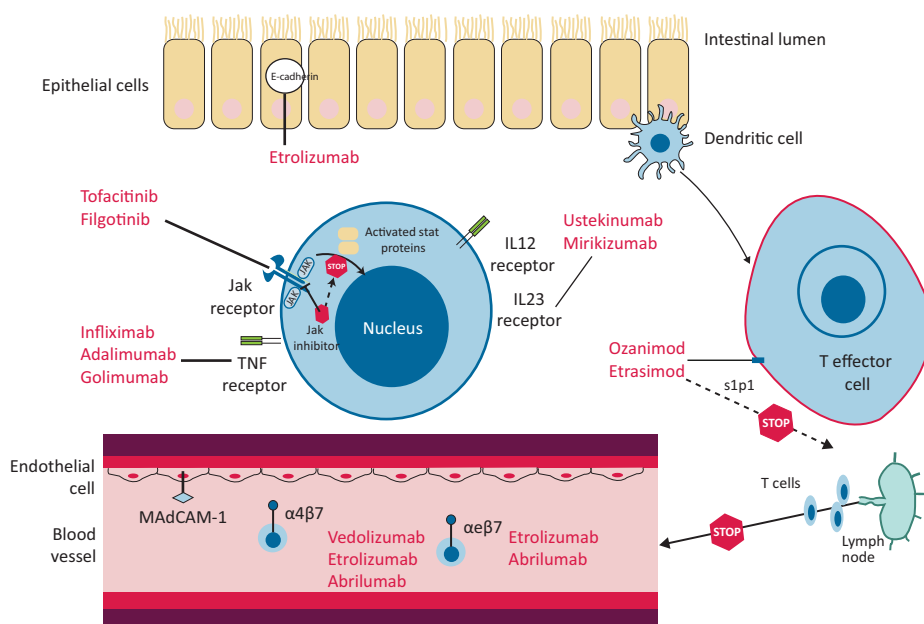
Prednisolone should be restricted to patients with moderate to severe UC of any disease extent or those who are unresponsive to standard therapy. Alternatively, for cases of mild to moderate UC, a multi-matrix formulation of budesonide (budesonide multi-matrix system (MMX)) was shown superior to placebo at a daily dose of 9 mg over an 8-week course.<sup>4</sup> Systemic adverse events of budesonide are considered fewer compared with conventional corticosteroids. Budesonide is not thought to induce adrenal suppression nor a significant reduction in bone mineral density.<sup>4</sup>

Thiopurines, such as azathioprine and mercaptopurine, have been used in maintenance of steroid-free remission. Thiopurines are associated with adverse events, with an estimated risk of 26% in a Spanish database study, including nausea (8%), hepatotoxicity (4%), myelotoxicity (4%), pancreatitis (4%), non-melanoma skin cancers and lymphomas. Assessment of

thiopurine methyltransferase (TPMT) status is recommended prior to thiopurine initiation, while measurements of thiopurine metabolites may be used in monitoring.<sup>4</sup>

Biologics have progressively changed the therapeutic landscape of UC (Fig 1). Choice of biologic agent depends on many factors, including route of administration, side effects, potential immunogenicity, speed of response to induction therapy, overall costs and availability of infusion facilities. Anti-tumour necrosis factor (TNF) drugs include intravenous infliximab originator and biosimilars, subcutaneous adalimumab originator and biosimilars, and subcutaneous golimumab. Primary response rates of infliximab in UC patients who failed standard therapy varied from 67% to 78% in real-world data.<sup>9</sup> Anti-TNF agents are preferred in patients with extra-intestinal manifestations of IBD, such as type 1 IBD-associated arthropathy, ankylosing spondylitis and pyoderma gangrenosum.<sup>10</sup> Formation of neutralising anti-drug antibodies is recognised as a reason for loss of response to anti-TNF drugs over time, which may be prevented by addition of an immunomodulator drug. Trials addressing combination therapy in UC have mostly studied the positive impact of combined infliximab and thiopurines; therefore, it is recommended that combination therapy with a thiopurine when infliximab is used as induction therapy for moderate to severe UC.<sup>4</sup> Serum drug and anti-drug antibody levels should be measured in patients considered to have lost response to an anti-TNF drug in order to guide therapeutic decision making (dose escalation or switch to a different anti-TNF or biologic class). The use of anti-TNF drugs may increase two-fold the pooled infectious risks (including tuberculosis, herpes zoster, cytomegalovirus among others (risk ratio (RR) 2.05; 95% CI 1.1–3.85)), thus justifying a pre-biologics screen for tuberculosis, HIV, herpes zoster and hepatitis B and C.<sup>11</sup>

Vedolizumab inhibits  $\alpha 4\beta 7$  integrin, thus decreasing leukocyte migration from the circulation into the bowel wall. Such a gut-selective pathway may explain the relative long-term safety of the drug.<sup>12</sup> In the GEMINI 1 study, response rates at week 6 were 47.1% in the vedolizumab group and 25.5% in the placebo group



**Fig 1. Mechanisms of action for biologics and small molecules used in ulcerative colitis.**  $\alpha 4\beta 7$  = alpha-4 beta-7 integrin;  $\alpha e 7$  = alpha-e beta-7 integrin; IL = interleukin; Jak = Janus kinase; MAdCAM-1 = mucosal vascular addressing cell adhesion molecule-1; s1p1 = sphingosine-1-phosphate receptor; Stat = signal transducer and activator of transcription; TNF = tumour necrosis factor.

( $p < 0.001$ ). For those who went into the maintenance trial, 41.8% who received 8-weekly vedolizumab and 44.8% who received vedolizumab every 4 weeks were in clinical remission compared with 15.9% in the placebo group at week 52 ( $p < 0.001$ ).<sup>13</sup> A head-to-head double-blind randomised controlled trial, the first to compare biologics in IBD between intravenous vedolizumab and subcutaneous adalimumab, showed higher rates of clinical remission and mucosal healing in the vedolizumab group at 52 weeks.<sup>14</sup>

Ustekinumab inhibits the p40 subunit of interleukins-12 and 23; in the UNIFI study, it was shown that 15.5% receiving ustekinumab achieved clinical remission at 8 weeks ( $p < 0.01$ ) compared with 5.3% receiving placebo. Of those who responded to induction, by week 44, 38.4% of those receiving ustekinumab every 12 weeks and 43.8% of those receiving ustekinumab every 8 weeks achieved clinical remission compared with 24% in the placebo group ( $p = 0.002$  and  $p < 0.001$ , respectively).<sup>15</sup> Clinical trial data suggest low rates of adverse events.<sup>16</sup>

Tofacitinib is an oral Janus kinase (JAK) inhibitor, which showed improvement in composite clinical/endoscopic outcomes in 16.6–18.5% of patients during the induction trials, compared with 3.6–8.2% of patients receiving placebo. At 1 year, remission was significantly higher in the treatment arms (34.3% in the 5 mg twice daily (BD) group and 40.6% in the 10 mg BD group), compared with 11.1% in the placebo group.<sup>17</sup> Adverse events include a higher risk of herpes zoster infection, justifying adequate zoster vaccination, and increased risk of venous thromboembolism (VTE) reported on the 10 mg BD dosing.<sup>18</sup> Higher doses should be avoided in patients considered at high risk of VTE.

### Follow-up and monitoring

Patient understanding and engagement in their care is crucial. Clinical parameters should be re-assessed every 3 months during the active phase. Once symptoms have resolved, clinical reviews should be performed every 6–12 months. Colonoscopies should be performed every 1–5 years to investigate suspected flares and to ensure surveillance of colorectal dysplasia, preferably with dye-spray chromoendoscopy.<sup>8</sup>

### Acute severe ulcerative colitis and surgical therapy including pouch implications

In the case of acute severe ulcerative colitis (according to the Truelove and Witts), the mainstay of treatment is intravenous steroids. For those not responding to intravenous steroids, a decision on day 3 is crucial using one of the various indices as a guide.<sup>4</sup> In this situation, either ciclosporin or infliximab maybe used as rescue therapy, with studies showing that there is no difference in efficacy.<sup>19</sup> Importantly, at the stage where rescue therapy is considered, it is imperative that surgical options are also explored.

The timing of surgical intervention in a patient with UC is multifactorial and needs to take into account disease severity and quality of life. In terms of acute severe ulcerative colitis that has not responded to medical therapy, a colectomy can be a life-saving procedure. For these patients who are offered surgery, a subtotal colectomy is the operation of choice. Surgical options include a permanent ileostomy, or restorative options to include the ileoanal pouch or, in some very selected cases, an ileorectal

anastomosis. Importantly, when considering surgical options for patients with ulcerative colitis it is important to involve the multidisciplinary team to include surgeons, stoma nurses, pouch nurses and dietitians to counsel patients about expectations from the surgical options.

### The future

There are a number of therapeutic targets being explored in the treatment of ulcerative colitis in various clinical phases to include sphingosine-1-phosphate receptor modulators (such as ozanimod and etrasimod), JAK inhibitors (such as upadacitinib), anti-leukocyte integrins (such as etrolizumab and abrilumab), monoclonal antibodies (such as mirikizumab) and faecal microbiota transplantation.<sup>20</sup> These potentially will offer new options for the medical treatment of ulcerative colitis, but currently remain at the clinical trial phase.

Head-to-head trials are likely to enable us to position biologics correctly. As we gain a better understanding of the biological mechanisms that drive UC, it may become possible to find the right drug for the right person at the right time, while also ensuring that the broader goals of the patient (impact on quality of life, psychological and dietary support) are addressed. ■

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