Medical therapies for ulcerative colitis

A practical update

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Ulcerative colitis is an increasingly prevalent inflammatory condition of the bowel that results in abdominal pain, diarrhoea, rectal bleeding and urgency. There are numerous new medications available for treating this chronic condition.

Ulcerative colitis is a chronic inflammatory bowel disease that primarily affects the colon.[1] A wide spectrum of disease patterns is seen in ulcerative colitis, varying from mild cases to patients who are refractory to medical therapy and require a colectomy to obtain disease control. Untreated inflammation can lead to significant morbidity, active extraintestinal manifestations of disease, mental health disorders, sexual dysfunction, nutritional abnormalities and the development of complications such as colonic dysmotility and colorectal cancer.[1,2]

Australia has one of the highest occurrences of ulcerative colitis globally.[3] An Australian general practice network study conducted between 2017 and 2019 found a crude prevalence rate of 334 per 100,000 people. This high prevalence, the expenses associated with treatment and the negative effect on young people engaging in study and work contribute to a substantial negative economic impact. In Australia, the estimated economic loss secondary to inflammatory bowel disease was estimated to be more than $3 billion in 2012.[4]

In recent years, there has been an expanding array of treatment options. This article is a practical primer on the modern medical management of ulcerative colitis.

KEY POINTS

- Ulcerative colitis is an inflammatory bowel disease primarily affecting the colon with associated comorbidities, including extraintestinal manifestations of disease, mental health disorders and reduced quality of life.
- Timely and appropriate medical therapy can alter the natural history of the disease and prevent complications of disease, such as motility issues and colorectal cancer.
- About half of all patients with ulcerative colitis respond well to 5-aminosalicylate therapy.
- Advanced therapies for ulcerative colitis have various mechanisms of action with very different safety profiles.
- Prednisolone is best used sparingly, with a preference to initiate and optimise treatment with advanced therapies.
- Biologic use in pregnancy is generally safe and often helps achieve good pregnancy outcomes; however, small molecules used for ulcerative colitis may be teratogenic.

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Medical therapy targets

Ulcerative colitis has a complicated and incompletely understood aetiology, with a combination of susceptible genetics, environmental factors (e.g. hygiene hypothesis and Western diet) and gut microbiome abnormalities culminating in immune dysregulation and inflammation of the colonic mucosa.[5] Proinflammatory cytokines

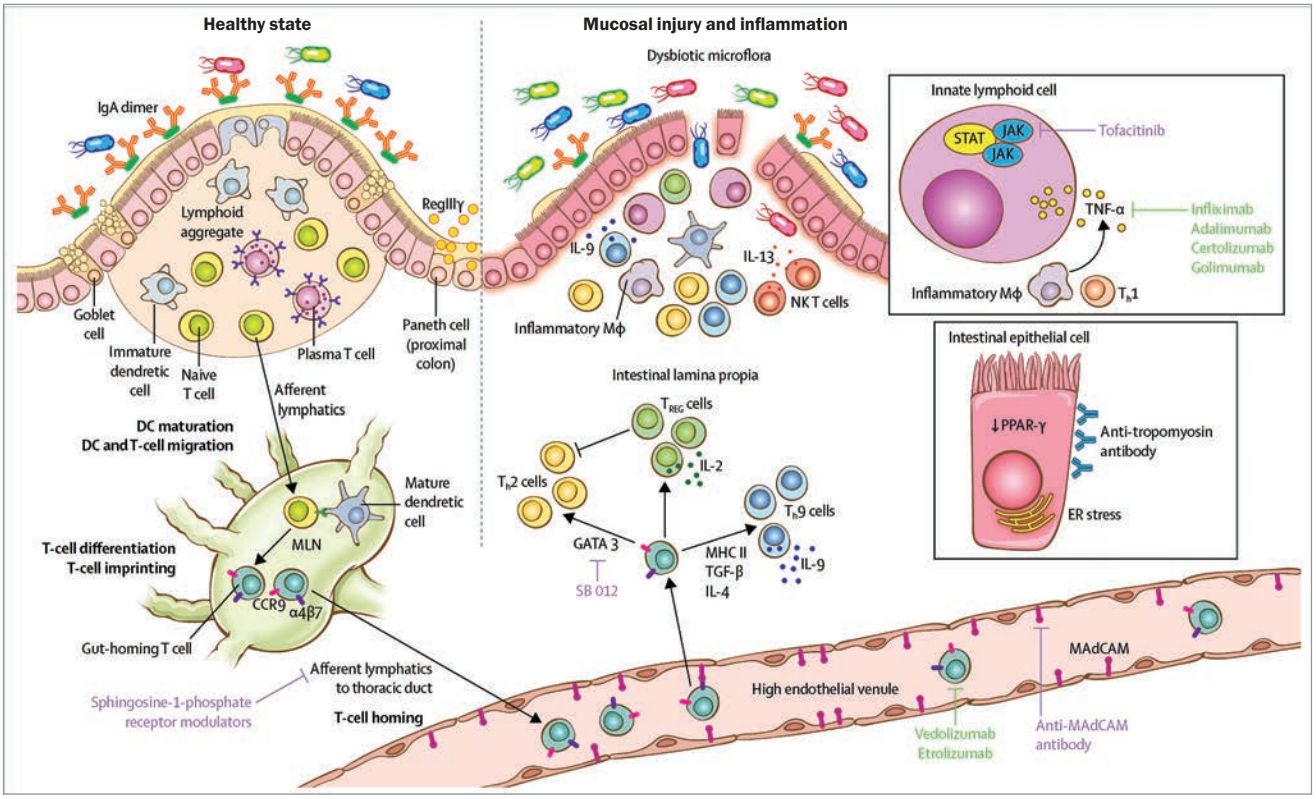

Figure. Overview of the intestinal immune system in patients with ulcerative colitis and therapeutic targets. Ulcerative colitis is associated with damage to the mucosal barrier (inset), allowing the luminal microflora to trigger a sustained and uninhibited inflammatory response. Mucosal injury and damage are associated with dysbiosis, which may contribute to the inflammatory cascade. The mechanisms of action of mesalazine (5-ASA) are incompletely understood but known to involve a reduction in colonic mucosal inflammation. Thiopurines (azathioprine, 6-mercaptopurine, and thioguanine) (not illustrated) inhibit lymphocyte proliferation, exert immunomodulatory effects on intestinal inflammation and reduce the trafficking of effector cells to the gastrointestinal tract. Corticosteroids have multiple mechanisms, including decreased vasodilation and permeability of capillaries, thus reducing lymphocyte trafficking as well as downregulating inflammatory cytokines. IL-12/23 inhibitors (ustekinumab, mirikizumab, risankizumab, guselkumab) (not illustrated) bind one of the subunits of IL-23, which ceases subsequent activation of the STAT inflammatory pathway. JAK inhibitors (tofacitinib, filgotinib and upadacitinib) selectively block JAK receptors, limiting signal transduction of the STAT signalling pathway and subsequent activation of numerous proinflammatory cytokines. Although certolizumab and etrolizumab feature in this figure, clinical trial data have not demonstrated significant efficacy for these drugs in ulcerative colitis; they are not TGA approved for use in patients with ulcerative colitis.

Abbreviations: 5-ASA = 5-aminosalicylate; DC = dendritic cell; ER = endoplasmic reticulum; IgA = immunoglobulin A; IL = interleukin; IFN = interferon; JAK = Janus kinase; Mφ = macrophage; MAdCAM = mucosal addressin cell-associated molecule; MHC = major histocompatibility complex; MLN=mesenteric lymph node; NK T cell = natural killer T cell; TGF = transforming growth factor; T_h = T-helper cell; T_{REG}=regulatory T cell.

underpin ongoing inflammation in the bowel (Figure).[1,5,6] Severe untreated inflammation can lead to dysmotility, stricturing, dysplasia and colorectal cancer.[1,2]

Medical therapy targets key mechanisms or cytokines in this inflammatory pathway and subsequently downregulates inflammation. The aims of therapy are to improve symptoms, improve quality of life, normalise markers of inflammation, prevent complications and disease progression and induce healing of the gut wall.[7]

Therapies for mild to moderate disease

5-aminosalicylates

About half of all patients with ulcerative colitis have a mild phenotype,[8] which can often be managed effectively with 5-aminosalicylate (5-ASA) therapy. Although the mechanism of action is unclear, 5-ASA therapies work topically, and downregulate colonic inflammation at the mucosal level.[9] The two main drugs that comprise 5-ASA therapy are sulfasalazine and mesalazine. Balsalazide (a pro-drug of mesalazine) has also been used historically. Mesalazine contains only 5-ASA, whereas sulfasalazine consists of two components: sulfapyridine and 5-ASA.

Sulfasalazine is initially converted to sulfapyridine and 5-ASA in the colon, where 5-ASA can exert its anti-inflammatory effects locally. Mesalazine delivers 5-ASA directly to the colon. Mesalazine has several advantages over sulfasalazine and is now the primary drug of choice. The benefits include once-daily dosing, as opposed to two to four times daily as required with

TABLE 1. PBS-LISTED 5-AMINOSALICYLATE THERAPIES FOR ULCERATIVE COLITIS

Medications	Preparations available	Release mechanism	Site of release	Induction dose*	Maintenance dose†
Asacol (mesalazine)	Enteric tablets	pH dependent	Terminal ileum to the colon	2.4–4.8 g daily	1.6–2.4 g daily
Colazide (balsalazide)	Capsules	Bacterial azo-reduction	Colon	Three 750-mg capsules three times daily	Two 750-mg capsules twice daily
Dipentum (olsalazine)	Capsules	Colonic bacterial splitting of aza-bond, converting olsalazine into 5-ASA	Colon	250 mg daily, with a gradual increase to 2 g daily (maximum 3 g, if tolerated)	1 g daily
Dipentum (olsalazine)	Tablets	Colonic bacterial splitting of aza-bond, converting olsalazine into 5-ASA	Colon	500 mg daily, with a gradual increase to 2 g daily (maximum 3 g, if tolerated)	1 g daily
Mesalazine 1.2 Takeda, Mesalz (mesalazine)	Modified-release tablets	Multimatrix system		2.4–4.8 g daily	2.4 g daily
Mesasal (mesalazine)	Enteric tablets	pH dependent	Mid-ileum to the colon	500 mg three times daily	250 mg three times daily
Mezavant (mesalazine)	Modified-release tablets	Multimatrix system	Terminal ileum and entire colon	2.4–4.8 g daily	2.4 g daily
Pyralin, Salazopyrin (sulfasalazine)	Enteric tablets	Bacterial splitting of diazo bond by colonic bacteria to 5-ASA and sulfapyridine	Colon	2 g twice daily	1 g twice daily
Pentasa (mesalazine)	Liquid enemas	N/A	Enema: left colon Suppository: rectum	1 g at night	Similar dose alternate nights
Pentasa (mesalazine)	Modified-release tablets Modified-release granules	Time dependent	Duodenum to the colon	4 g daily	2 g daily
Salofalk (mesalazine)	Enteric tablets Modified-release granules	pH dependent	Tablets: mid-ileum to the colon Granules: left colon	1.5–3 g daily	1.5 g daily
Salofalk (mesalazine)	Liquid or foam enemas	N/A	Enema: left colon Suppository: rectum	Enema: 2 g at night Suppository: 1 g nocte	Similar dose alternate nights

Abbreviation: 5-ASA = 5-aminosalicylate.

*Typical induction dose for a period of eight to 12 weeks for oral therapy and four to eight weeks for rectal therapy.

†Typical maintenance doses.

sulfasalazine. Furthermore, side effects with mesalazine are uncommon, whereas sulfasalazine can cause nausea, vomiting and headaches because of allergies associated with sulfapyridine. Sulfasalazine can cause reversible oligospermia that can be associated with fertility issues.[10,11] However, sulfasalazine is more effective for enteropathic arthritis and is often used in patients with concomitant ulcerative colitis and enteropathic arthritis.[12]

Mesalazine has numerous formulations (Table 1), including oral and topical (per rectal) therapies.[13-17] The oral therapies have different mechanisms of release.[14] Choosing the appropriate preparation may be important as the timing of release will differ, with some formulations commencing release in the small bowel and others commencing release in the left colon. This may be clinically important as patients with extensive disease may respond better to a pan-colonic preparation, and there is evidence to suggest that patients with distal colitis respond better to granule preparations; however, this is debated.[18] The oral formulations have a high dose induction, followed by a lower maintenance dose. Some patients will be prescribed high-dose mesalazine indefinitely as they relapse on low-dose mesalazine.

In addition to oral preparations, rectal topical preparations of mesalazine are

available, including suppositories and enemas. The extent of an enema's action is the sigmoid and perhaps the descending colon, whereas suppositories will only treat the rectum, but are usually more tolerable by patients to self-administer than enemas. The evidence suggests that patients respond better to both 'top and bottom' therapy, as oral preparations may not deliver an adequate amount of the drug to the distal colon, as well as the rectum in particular.[17] The largest hurdle to rectal therapies is patient reluctance, particularly in the long term. Therefore, a commonly used strategy in clinical practice is to use rectal therapies alongside oral therapies for inducing remission and then tailoring off the rectal therapy as tolerated to maintain disease control. For patients with a proctitis phenotype, suppository therapy is usually more effective than oral therapy and reducing the suppository therapy to three times a week when well can often lead to success in achieving a balance between receiving therapy and the inconvenience of rectal preparations.[17]

In addition to treating inflammation, evidence suggests that mesalazine has a chemopreventive action against bowel cancer. It is unclear if this chemopreventive effect is secondary to, or independent of, the drug's ability to treat inflammation.[19] This is a favourable benefit, given the increased risk of colorectal cancer in patients with ulcerative colitis.

Overall, mesalazine is considered a safe drug and is usually well tolerated.[20] Patients are not immunocompromised on these medications. Rare but serious complications can occur including interstitial nephritis and numerous hypersensitivity reactions, such as pancreatitis, pericarditis, myocarditis, pneumonitis, hepatitis and hematological abnormalities. There is a one in 400 risk of developing interstitial nephritis and hence, three-monthly monitoring with a basic blood panel (including a full blood count; liver function tests; C-reactive protein level measurement; and urea, electrolytes and creatinine tests) for the first six months followed by six- to 12-monthly monitoring is recommended.[20]

In summary, 5-ASA therapies are safe, inexpensive and effective medications for the management of mild to moderate ulcerative colitis.

Thiopurines

Thiopurines, such as azathioprine and 6-mercaptopurine, are small molecules that inhibit lymphocyte proliferation, exert immunomodulatory effects on intestinal inflammation and reduce the trafficking of effector cells to the gastrointestinal tract.[21] Thiopurines are used as maintenance therapy in patients with mild to moderate ulcerative colitis after failure to respond to mesalazine or as combination therapy with an antitumour necrosis factor (TNF) agent to prevent antibody formation and improve serum drug levels.[17,21]

However, the use of thiopurines purely for the treatment of ulcerative colitis is becoming less desirable. Thiopurines have a significant toxicity profile including the cumulative risk of nonmelanomatous skin cancer, urothelial cancer, cervical cancer and lymphoma.[22] Advanced therapies are more effective, often better tolerated and, generally speaking, have more attractive safety profiles than thiopurines.[17] In addition, the initial monitoring and dose titration for thiopurines can make them more challenging to prescribe. The main barrier to using advanced therapies rather than thiopurines is the substantial cost difference. Patients with ulcerative colitis are eligible for an advanced therapy on the PBS if they have inadequate disease control after three months on a thiopurine (full dose) or if they are intolerant to thiopurines.

Methotrexate

Unlike in Crohn's disease, methotrexate is not an effective treatment for ulcerative colitis;[23] however, methotrexate can be used off label in combination with anti-TNF therapy to prevent antibody formation against anti-TNF therapies. Methotrexate is commonly prescribed for the treatment of numerous extraintestinal manifestations of inflammatory bowel disease, such as enteropathic arthritis.[21]

Advanced therapies for moderate to severe disease

A substantial proportion of patients will either fail to respond to mesalazine (42% in one study)[24] and thiopurine therapy, subsequently lose response to therapy, or present with severe disease and require an advanced therapy upfront. Recently, there has been a significant expansion of the number of medications demonstrating efficacy in moderate to severe ulcerative colitis, and several of these have obtained PBS approval. An overview of all therapies for ulcerative colitis is presented in Table 2, with monitoring and screening strategies presented in Table 3.[17,25]

Biologic therapies

Anti-integrin therapies

Anti-integrin therapies block lymphocyte trafficking to the gut, thereby preventing the associated inflammation lymphocytes cause in cases of ulcerative colitis.[1] Vedolizumab is a gut-selective anti-integrin (α4β7 integrin blocker) and is the only PBS-listed anti-integrin therapy for ulcerative colitis. Although head-to-head studies are lacking, vedolizumab was shown to have the best long-term persistence (a surrogate marker of effectiveness) of all advanced therapies in a large, multicentre, UK-based ulcerative colitis cohort.[26]

In addition to its clinical utility, vedolizumab has an excellent safety profile, given it is a gut-selective immunosuppressant.[27] A network meta-analysis showed that vedolizumab has the best safety profile compared with other advanced therapies for ulcerative colitis.[28] Vedolizumab is usually well tolerated with similar general common side effects experienced with most biologic therapies. Vedolizumab is administered by intravenous induction, followed by either eight-weekly intravenous infusions or fortnightly subcutaneous injections for maintenance therapy.

TABLE 2. OVERVIEW OF MEDICAL THERAPIES FOR ULCERATIVE COLITIS[17]

Medication	TGA indications or ECCO guideline recommendations	Adverse effects of interest	Suggested maintenance dosing*	Notes
5-aminosalicylate therapies (balsalazide, mesalazine, olsalazine, sulfasalazine)	• Induction and maintenance of remission in patients with mild to moderate, active UC • Balsalazide and olsalazine are indicated in patients who are intolerant to sulfasalazine	• Interstitial nephritis (rare) • Hypersensitivity reactions (rare) • Usually minimal and well tolerated	• See Table 1	• Good safety profile • May reduce the risk of developing bowel cancer
Thiopurines (azathioprine)	• Monotherapy for the induction of remission in patients with active UC† • Maintenance of remission in patients with steroid-dependent UC or who are intolerant to 5-aminosalicylates†	• GI upset • Myelosuppression • Abnormal LFT results • Pancreatitis • Nonmelanomatous skin cancer • Urothelial cancer	• Azathioprine: 2–2.5 mg/kg daily (oral) • 6-mercaptopurine: 1–1.5 mg/kg daily (oral)	• Measure TPMT before starting and measure thiopurine metabolites at 8 weeks after starting therapy
Anti-integrin therapies (vedolizumab)	• Moderate to severe UC in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a TNF-α antagonist	• No specific adverse effects§	• 8 weekly (intravenous) • 105 mg fortnightly (SC)	• Gut-specific therapy
IL-12/23 and IL-23 inhibitors (ustekinumab, mirikizumab, risankizumab, guselkumab)	• Moderately to severely active UC in patients who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or biologic therapy	• No specific adverse effects§	• Ustekinumab: 90 mg SC, 8 weekly • Mirikizumab: 200 mg SC, 4 weekly • Guselkumab: 100–200 mg SC, 4–8 weekly • Risankizumab: 180–360 mg SC, 8 weekly	• Good safety profile • Mirikizumab, risankizumab and guselkumab are not yet PBS listed for the treatment of UC or inflammatory bowel disease
Anti-TNF agents (infliximab, adalimumab, golimumab)	• Moderate to severe UC in patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 6–8 weeks of treatment to continue treatment beyond that time	• Increased risk of severe opportunistic infections • Drug-induced lupus • Demyelinating lesions	• Infliximab: 5 mg/kg 8 weekly (intravenous) • Infliximab: 120 mg fortnightly (SC) • Adalimumab: 40 mg fortnightly • Golimumab: 100 mg 4 weekly	• Avoid in patients with heart failure and demyelinating conditions • Covers almost all EIMs • Best for perianal disease
JAK inhibitors (filgotinib, upadacitinib, tofacitinib)	• Moderately to severely active UC in patients who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biological medicine	• Increased cardiovascular and venous thromboembolism risk • Acne • Shingles • Hypercholesterolaemia	• Filgotinib: 200 mg daily • Upadacitinib: 15 mg or 30 mg daily • Tofacitinib: 5 mg or 10 mg daily	• Filgotinib is not TGA approved • Fast acting • Good for EIMs • Good in patients who have failed anti-TNF agents • Avoid in patients with high cardiovascular risk

Abbreviations: ECCO = European Crohn's and Colitis Organisation; EIM = extraintestinal manifestations of disease; GI = gastrointestinal; IFX = infliximab; IV = intravenous; JAK = Janus kinase; LFT = liver function test; MMX = multimatrix system; PBS = Pharmaceutical Benefits Scheme; TNF = tumour necrosis factor; TPMT = thiopurine methyltransferase; SC = subcutaneous; UC = ulcerative colitis.

* Dosing can vary substantially and depends on the clinical context and purpose of the medication. This provides a standard dosing regimen. Listed dosing for biologics is maintenance dosing regimens.

† Recommendation as per the ECCO guidelines.[17]

‡ With extended use of three months or more, or with multiple courses of corticosteroids.

§ All biologics, including intravenous and subcutaneous medications, have a side effect profile; however, these medications demonstrate no additional safety specific concerns.

TABLE 2. OVERVIEW OF MEDICAL THERAPIES FOR ULCERATIVE COLITIS[17] *continued*

Medication	TGA indications or ECCO guideline recommendations	Adverse effects of interest	Suggested maintenance dosing*	Notes
Sphingosine-1 phosphate receptor modulators (ozanimod, etrasimod)	• Moderately to severely active UC in patients who have had an inadequate response, lost response, or were intolerant to either conventional, biologic or JAK inhibitor therapy	• Hypertension • Cardiac conduction abnormalities • Macular degeneration • Lymphopenia	• Ozanimod: 0.92 mg daily • Etrasimod: 2 mg daily	• Avoid in patients with IHD or cardiac conduction abnormalities • Screen for macular degeneration in patients with diabetes • Conduct ECG and measure BP before starting
Glucocorticoids (prednisolone)	• Induction of remission in patients with moderately-to-severely active UC†	• Acne • Weight gain • Mood disturbance • Striae • Thin skin • Muscle atrophy • GI upset • Negative affect on bone mineral density‡	• 40 mg for one week, 30 mg for one week, then wean by 5 mg weekly thereafter (oral)	• To be used sparingly • Alternative options include an advanced therapy or budesonide in some cases
Budesonide MMX 9 mg	• Induction of remission in patients with mild to moderate active UC where 5-aminosalicylate treatment is not sufficient or not tolerated	• Usually minimal given extensive first-pass hepatic metabolism	• 9 mg daily for 8 weeks (oral)	• Not PBS listed

Abbreviations: ECCO = European Crohn's and Colitis Organisation; EIM = extraintestinal manifestations of disease; GI = gastrointestinal; IFX = infliximab; IV = intravenous; JAK = Janus kinase; LFT = liver function test; MMX = multimatrix system; PBS = Pharmaceutical Benefits Scheme; TNF = tumour necrosis factor; TPMT = thiopurine methyltransferase; SC = subcutaneous; UC = ulcerative colitis.

* Dosing can vary substantially and depends on the clinical context and purpose of the medication. This provides a standard dosing regimen. Listed dosing for biologics is maintenance dosing regimens.

† Recommendation as per the ECCO guidelines.[17]

‡ With extended use of three months or more, or with multiple courses of corticosteroids.

§ All biologics, including intravenous and subcutaneous medications, have a side effect profile; however, these medications demonstrate no additional safety specific concerns.

Vedolizumab is frequently used in patients with ulcerative colitis and often as the first-line advanced therapy, given its efficacy, persistence and excellent safety profile. Vedolizumab often does not work as rapidly as other advanced therapies (anti-TNF and Janus kinase [JAK] inhibitors, in particular) and patients may require corticosteroids or a calcineurin inhibitor as concomitant bridging therapy if they are highly symptomatic or have severe inflammation.[29,30] Given that vedolizumab is a gut-selective immunosuppressant, patients with extraintestinal manifestations of disease do not respond well, unless the manifestations are promoted by underlying disease activity, such as some cases of enteropathic arthritis.[12] Additionally, vedolizumab is not as effective after previous failure to respond to anti-TNF agents.[1]

Interleukin-12/23 and interleukin-23 inhibitors

Interleukin (IL)-23 is one of the chief proinflammatory cytokines involved in the pathogenesis and continuing inflammation of ulcerative colitis.[31] The first approved and PBS-listed interleukin therapy for ulcerative colitis was ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23.[32] Subsequently, specific IL-23 inhibitors, which target the p19 subunit of IL-23, have demonstrated efficacy in phase 2 and some phase 3 trials.[33,34] These include mirikizumab, risankizumab and guselkumab, although these are not yet PBS listed for the treatment of ulcerative colitis or inflammatory bowel disease. Some of these agents are administered by intravenous infusions for induction; however, they are all administered subcutaneously for maintenance therapy.

There are numerous strengths to IL inhibitors. They are often effective in treating numerous extraintestinal manifestations and concomitant autoimmune conditions, such as psoriasis and peripheral small joint arthritis.[12] They are usually well tolerated and possess a good safety profile, with studies suggesting no increased risk of infection or malignancy.[27] Similar to vedolizumab, they have good persistence rates once they induce remission. In the setting of failing to respond to anti-TNF agents, they may have greater efficacy compared with vedolizumab.[1]

Antitumour necrosis factor-α agents

TNF-α is another a key proinflammatory cytokine implicated in the pathogenesis and ongoing inflammation of ulcerative colitis.[35] Anti-TNF agents are monoclonal antibodies directed against TNF-α.

Infliximab, adalimumab and golimumab are the only anti-TNF therapies to have demonstrated efficacy in ulcerative colitis, with the literature suggesting infliximab may be the most effective of the anti-TNF therapies.[1,28,36] Golimumab and adalimumab are PBS listed for moderate to severe ulcerative colitis, and infliximab for acute severe and moderate to severe ulcerative colitis.

Anti-TNF agents tend to work quickly, enabling relatively quick symptom improvement.[37] Anti-TNF agents are very useful in patients with extraintestinal manifestations of inflammatory bowel disease or concomitant autoimmune disorders, as TNF-α plays an important role in these associated conditions.[12] Anti-TNF agents are often useful for managing dermatological, arthritic and ophthalmological manifestations. Infliximab is considered one of the most effective medications for patients with severe disease, and is often used as first-line rescue therapy in patients with acute severe ulcerative colitis who have failed to respond to intravenous corticosteroids.[38]

However, there are some limitations with anti-TNF agents. They pose the risk of the immune system developing neutralising antidrug antibodies, which often limits the long-term durability of the drug.[39] Concomitant therapy with thiopurines or methotrexate can reduce this risk, but may come with the additional side effects of these medications.[22] The potential long-term problems of additional immunomodulator therapy can be reduced when the immunomodulators are used for six to 24 months, mitigating the risk where neutralising antibody formation is the highest.[40]

Anti-TNF agents exert mild to moderate immunosuppressive effects.[27] There is an increased relative risk of lymphoma and skin cancer, particularly when used in combination with a thiopurine. Lastly, anti-TNF agents can have some rare but serious side effects (including demyelination), worsen heart failure and cause drug-induced lupus. Most patients will tolerate anti-TNF agents quite well in clinical practice; however, caution should be applied in treating older patients or those with more comorbidities.

In summary, anti-TNF agents remain a key advanced therapy for ulcerative colitis, particularly in patients with severe disease and those with extraintestinal manifestations. However, the safety profile and possible need for concomitant immunomodulator therapy may lend itself to be a less attractive option in some patients.

Small molecules

Numerous small molecules are now available for the treatment of moderate to severe ulcerative colitis. These have numerous benefits including additional modes of action and oral drug administration, reducing the burden on outpatient infusion services.

Janus kinase inhibitors

JAK inhibitors block JAK receptors, limiting signal transduction of the STAT signalling pathway and subsequent activation of numerous proinflammatory cytokines. There are two TGA-approved and PBS-listed JAK inhibitor therapies for moderate to severe ulcerative colitis: tofacitinib and upadacitinib.[41] Tofacitinib selectively blocks JAK1 and JAK3 receptors, whereas filgotinib and upadacitinib selectively block JAK1.

Tofacitinib and upadacitinib are effective for inducing remission and improving symptoms rapidly.[28,42] This has led to the hypothesis that this class may eventually replace corticosteroids for induction therapy. Further, considering their rapid onset of action, their role in the acute severe ulcerative colitis setting is being explored currently.[43] In addition, these medications tend to work similarly well whether the patient is naïve to advanced therapies or have failed to respond to other advanced therapies.[44-45] This is helpful for clinicians given that subsequent advanced therapies (particularly after failure to respond to anti-TNF agents) have diminishing efficacy in achieving and maintaining disease remission. There are also emerging data on the use of JAK inhibitors in the acute severe ulcerative colitis setting, providing additional key therapies where only ciclosporin and infliximab have previously been recognised as efficacious rescue therapies.[38,46] JAK inhibitors are effective in patients with extraintestinal manifestations of disease or concomitant immune-mediated disorders.[12] Tofacitinib and upadacitinib have numerous dosing ranges, and they can be up- or down-titrated depending on the clinical response.[47,48] However, at higher doses, there is an increased risk of side effects, as other JAK receptors (JAK2, JAK3 and tyrosine kinase-2) may be blocked.[49]

There are numerous recognised safety concerns associated with JAK inhibitors, including an increased risk of infection, shingles, hypercholesterolaemia, major adverse cardiovascular events, malignancy and venous thromboembolism.[22,49] These risks are generally heightened with advanced age and most safety data are based on patients with rheumatoid arthritis.[50] This is important to contextualise, given that patients with rheumatoid arthritis have a different underlying pathophysiology, are usually older and have more comorbidities compared with patients with ulcerative colitis. Importantly, the increased risk of cancer and cardiovascular disease has primarily been seen among those with an increased cardiovascular risk or known cardiovascular disease.[50] Therefore, safety risks must be contextualised to individual patients.

In summary, JAK inhibitors are a fast-acting and efficacious class of medication, which may limit corticosteroid use and work well for patients with extraintestinal manifestations and those who have failed to respond to previous therapies. However, they do come with important safety concerns.

Sphingosine-1 phosphate receptor modulators

Sphingosine-1 phosphate (S1P) receptor modulators have been used in patients with multiple sclerosis for some time now

TABLE 3. MONITORING FOR ADVERSE EVENTS WHILE A PATIENT IS RECEIVING THERAPY FOR ULCERATIVE COLITIS

Medication	Blood monitoring*	Imaging monitoring	Preventive health	Preventive strategies†
Prednisolone	• N/A	• DEXA scan if course longer than 3 months or recurrent prednisolone courses	• Dietary measures, given risk of weight gain • Monitor for mood disturbances, and blood pressure and glycated haemoglobin abnormalities	• Use of concomitant calcium and vitamin D supplementation
Budesonide MMX 9 mg	• N/A	• Usually N/A‡	• Usually N/A	• Usually N/A
Thiopurines	• Fortnightly blood tests while initiating therapy; 3-monthly thereafter	• N/A	• Annual skin checks for nonmelanomatous skin cancers • 3-yearly cervical cancer screening	• Sun safety measures
Anti-TNF agents	• 3–6 monthly	• N/A	• Consider skin checks§	• Recombinant zoster vaccine‡
IL-23 inhibitors	• 6 monthly	• N/A	• N/A	• N/A
JAK inhibitors	• 3–6 monthly	• N/A	• Monitoring and management of CV risk factors	• Manage CV risk factors • VTE prevention measures • Recombinant zoster vaccine‡
S1P receptor modulators	• 3–6 monthly	• N/A	• Monitor blood pressure and heart rate	• Recombinant zoster vaccine‡
Vedolizumab	• 6 monthly	• N/A	• N/A	• N/A

Abbreviations: BP = blood pressure; CV = cardiovascular; DEXA = dual-energy x-ray absorptiometry; HR = heart rate; JAK = Janus kinase; MMX = multimatrix system; N/A = not applicable; S1P = sphingosine-1 phosphate; VTE = venous thromboembolism.

* Routine monitoring of bloods includes: a full blood count; urea, electrolytes and creatinine levels; liver function tests; and C-reaction protein levels.

† These are additional health strategies beyond general health measures such as vaccination, routine skin checks, and national cancer screening programs. All patients on immunosuppressive therapy will benefit from discussing a program of skin checks with their GP and tailoring frequency based on additional individual risk factors.[25]

‡ Budesonide usually has low systemic absorption; however, some patients do develop significant systemic absorption as demonstrated by classic glucocorticoid symptoms. In this case, monitoring used for traditional glucocorticoids may be appropriate, particularly for prolonged courses.

§ Particularly important for those over the age of 50 years.

but have now emerged as an efficacious treatment for ulcerative colitis.[51,52] S1P receptor modulators sequester subsets of lymphocytes in peripheral lymph nodes, preventing them from trafficking to areas of inflammation. This is highly useful in ulcerative colitis, given there are high levels of T lymphocytes typically driving inflammation in active disease.

There are two PBS-listed S1P receptor modulators indicated for ulcerative colitis: ozanimod and etrasimod. Ozanimod is a selective $S1P_{1,5}$ receptor modulator, and etrasimod is a newer-generation $S1P_1$,[4,5] receptor modulator.[53] The benefits of this class include a different mechanism of action, targeting lymphocytes, rather than cytokines, which is particularly useful in patients with concomitant multiple sclerosis.

Regarding safety, ozanimod and etrasimod are newer and more selective molecules than the original S1P receptor modulators and are therefore associated with fewer side effects than the original generation (e.g. fingolimod used for multiple sclerosis).[53] S1P receptor modulators are associated with functional lymphopenia (wherein the lymphocytes are still present in the body but not circulating), which can increase the risk of infection. Trial data have not demonstrated a significantly increased risk of infection in patients with ulcerative colitis, but the occurrence of infection is higher than with some of the other advanced therapies.[28,53] Macular degeneration is also a safety consideration; therefore, patients with risk factors for macular disease, in particular patients with diabetes, should be reviewed by their optometrist or ophthalmologist before starting therapy.[54]

S1P receptor modulators have been associated with cardiac conduction abnormalities. Notably, trial data for ozanimod and etrasimod have not demonstrated an increased risk of cardiac conduction abnormalities, except bradycardia when first introducing ozanimod, but not estrasmiod.[53] It is recommended that all patients should undergo an ECG to rule out sinus or AV nodal disease prior to commencing this class of medication. S1P receptor modulators are generally avoided in patients with ischaemic heart disease or cardiac conduction abnormalities.[27] Additionally, this class of drugs can cause hypertension and, rarely, malignant hypertension; therefore, patients should have normal or treated blood pressure

before starting therapy, with arrangements made for monitoring blood pressure while on the medication.[54]

In summary, S1P receptor modulators are a novel class of therapy in the ulcerative colitis space, ideal for patients with concomitant multiple sclerosis and convenient to administer. However, they have specific cardiovascular and ophthalmological screening and monitoring requirements.

Safety and monitoring of advanced therapies

Adverse events of interest and monitoring requirements are summarised in Table 2 and Table 3.[17,25] The PBS require re-application for advanced therapies on a six-monthly basis. This is often an ideal time to perform monitoring, particularly basic blood monitoring. Given the variety of safety and monitoring requirements, ranging from additional vaccinations to monitoring bone health, it is important that all healthcare professionals involved in caring for patients with ulcerative colitis are mindful of preventive health strategies to achieve best outcomes.

Pregnancy

Overall data suggest that biologic therapy is safe in pregnancy and should be continued given the importance of maintaining good disease control throughout pregnancy to optimise outcomes.[55] Studies have not demonstrated an increased risk of infection in the first 12 months of life in babies born to mothers on biologic therapy. Live vaccines should not be given in the first six months to babies born to mothers on vedolizumab and IL-23 therapy, and the first 12 months for babies born to mothers on anti-TNF therapy. The only vaccine on the National Immunisation Program schedule this currently affects is the rotavirus vaccine.[56]

Unlike biologics, small molecules should be avoided in pregnancy and are usually discontinued before conception.[55] This recommendation on small molecules is primarily based on animal data, which show increased fetal death and malformation; however, there are limited human data currently. The potential risk of teratogenicity of small molecules must be discussed with women of childbearing age and effective contraception strategies should be put in place. Regarding immunomodulators, thiopurines can be continued throughout pregnancy; however, they should not be started during pregnancy in case a serious complication emerges, such as pancreatitis.[55] Methotrexate is teratogenic and should ideally be discontinued three months before conception.[21]

The modern role of corticosteroids

Glucocorticoids still maintain a role in inducing remission in patients with moderate to severe disease.[17] However, prolonged use or recurrent use of corticosteroids is best avoided given the significant side effect profile, with some side effects, such as bone mineral density loss, having a cumulative effect.[27] Initiation, optimisation or switching of advanced therapies is often a preferable strategy to manage ulcerative colitis flares.

One strategy to limit the burden of corticosteroids is to use budesonide multimatrix system (MMX) 9 mg, a locally acting glucocorticoid that undergoes extensive hepatic first-pass metabolism, minimising systemic exposure to corticosteroids.[17] A limitation of budesonide MMX 9 mg is that the colonic release formulations tend to be more effective in the left colon and, therefore, may not work as well in pan-colonic disease.[57] Budesonide is TGA approved for mild to moderate disease, but not moderate to severe disease.[17,57] The drug is not PBS listed for the indication of ulcerative colitis; however, numerous tertiary inflammatory bowel disease units will have access to prescribing this drug through their hospital pharmacy. In additional to oral corticosteroids, rectal preparations (e.g. prednisolone suppositories, budesonide enemas) have additional benefits to oral therapies alone and are a useful addition for patients who experience flares.[58]

The future of medical therapies

There remains a requirement to improve therapeutic strategies for moderate to severe ulcerative colitis. Remission rates for advanced therapies in clinical trials vary from 30 to 60% for moderate to severe disease, meaning many patients fail to achieve remission with medical therapy alone.[59] Promising strategies to improve medical outcomes include novel therapies, dual biologic treatments and faecal microbial transplants.[25,60-62] The latter holds significant promise; however, there are several barriers to implementation including setting up appropriate donor banks and systems, along with the intensive and expensive nature of delivering the therapy (endoscopically in numerous trials). However, further studies are in place, investigating the use of oral faecal microbial transplants as an induction and maintenance therapy for inflammatory bowel disease.[63]

Conclusion

The management of ulcerative colitis encompasses a wide array of medical therapies, each tailored to the severity of the disease. 5-ASA therapy stands out as a viable option for mild cases, offering effective symptom control and disease management. However, for moderate to severe disease, advanced therapies emerge as the preferred choice, offering greater efficacy in achieving disease remission and improving patients' quality of life. Continued research and clinical evaluation of these therapies are imperative to refine treatment strategies and optimise outcomes for individuals with ulcerative colitis. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Medical therapies for ulcerative colitis

A practical update

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