

New Zealand Society of Gastroenterology Guidelines for the Management of Refractory Ulcerative Colitis

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ABSTRACT

The management of patients with ulcerative colitis who are dependent on corticosteroid for control of symptoms, or refractory to corticosteroids or standard immunosuppressive therapy, is challenging. The development of newer medical therapies has increased the options for managing patients in this situation, but access and funding remain limited. This guideline summarises the literature regarding this situation and provides guidance as to the management of refractory colitis in the New Zealand setting.

Ulcerative colitis is a chronic inflammatory condition of unknown aetiology typically causing continuous, non-granulomatous mucosal inflammation of the colon. It affects the rectum and a variable extent of the colon in continuity. The disease is characterised by a relapsing, remitting course leading to bloody diarrhoea, cramping and abdominal pain.¹

Due to the limited knowledge of the underlying cause, current drug treatments are empiric, aimed at controlling the inflammatory process and are not curative. First-line therapy for mild to moderate disease focuses on the use of 5-aminosalicylic acid (5ASA) preparations, depending on the extent of the disease, either in a topical formulation per rectum or as tablets. For disease refractory to 5ASA and for more severe disease, immunomodulating or suppressing medicines become necessary. Because of their rapidity of action and effectiveness, corticosteroids are often used as first-line immunosuppressants, usually as a bridge to agents of slower onset, such as the immunomodulator 6-Mercaptopurine, or its prodrug, Azathioprine.

The goals of treatment include induction and maintenance of remission of symptoms and of mucosal inflammation, which can be assessed by clinical examination,

normalisation of blood tests and endoscopic assessment looking at mucosal healing. Long-term goals would include improvement in quality of life and minimisation of cancer risk. An important tenet of modern disease management is the reduction of the need for long-term corticosteroids.² Even though corticosteroids can be beneficial in inducing remission, they are associated with side effects. Early adverse effects include cosmetic side effects (such as acne, moon facies, weight gain and oedema), sleep and mood disturbance, glucose intolerance and dyspepsia. Dose related effects with prolonged use (usually >12 weeks of use) include cataracts, osteoporosis and osteonecrosis of the femoral head, myopathy and susceptibility to infections. Despite this, 25% of patients one year after diagnosis are dependent on corticosteroids for control of disease, and it is not uncommon for disease to be refractory to first-line immunosuppressant agents.³ Patients in this situation are said to have “refractory” colitis. The focus of this practise guideline is to raise awareness of the importance of identifying the “refractory” patients early, and to provide information and guidance regarding the options available in New Zealand for escalation of therapy.

Definitions

Refractory ulcerative colitis comprises patients in 3 main situations: Steroid refractory; steroid dependent; and standard immunomodulator (Azathioprine/6-Mercaptopurine) refractory disease. For the purpose of this guideline, these groups will be defined using the ECCO consensus statement⁴

- *Steroid refractory colitis*: Patients who have active disease, despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks
- *Steroid dependent colitis*: Patients who either are unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrence of disease activity, or who relapse within 3 months of stopping steroids
- *Immunomodulator refractory colitis*: Patients who have active disease or relapse in spite of thiopurines at an appropriate dose for at least 3 months (i.e. azathioprine 2–2.5 mg/kg/day or mercaptopurine 0.75–1 mg/kg/day in the absence of leukopenia)

Clinical assessment of severity

For the purposes of this guideline, “clinically active disease” is defined as disease where the treating clinician has evidence to suggest there is ongoing inflammatory disease, either because of documented mucosal inflammation or symptoms consistent with ongoing inflammation. The treatment decisions required in the setting of refractory colitis are weighty and it is often reasonable, in the first instance, to ensure after clinical assessment and basic laboratory investigations:

1. That adherence to medications is adequate
2. Adequate delivery of medication to the mucosa
3. Absence of concurrent disease (eg, proximal constipation or superimposed infection)
4. Concomitant diseases that might contribute to symptoms (eg, irritable bowel syndrome and coeliac disease) have been ruled out

5. Confirmation that it is UC and that Crohn’s disease has been excluded
6. Stool cultures to exclude the presence of pathogenic organisms including *Clostridium difficile*, *Giardia lamblia* and other common causes of infectious diarrhoea should generally be undertaken
7. Endoscopic assessment with flexible sigmoidoscopy is often warranted. As well as allowing objective assessment of the degree of inflammation, endoscopy allows microscopic and immunohistochemical assessment of mucosal biopsies for CMV infection. Colonoscopy may be indicated if the extent of the disease is unknown or there are concerns it may have altered.

Often, response to therapy is evident. However, the objective scoring of disease activity aids decision making, particularly if there are delays between decision points or if multiple clinicians are involved in decision making. A commonly used scoring system for the assessment of the clinical activity of colitis in the New Zealand setting is the simple colitis activity index (Table 1).⁵ This score defines remission as less than 3 points. A score of 4 or more is required for public funding of infliximab for UC in New Zealand.

Additional tools that can be used to monitor activity, include biochemical or laboratory markers such as C-reactive protein (CRP) and faecal calprotectin (FC). CRP has the advantage of being freely available, with result provided rapidly. FC is a heat-stable protein released into the intestinal lumen as a consequence of leukocyte trafficking to the gut. It has the disadvantage of being slow to process. CRP and FC are predictive of endoscopic disease activity; however, no lower threshold has been identified that reliably predicts mucosal healing by strict criteria.⁶ At this stage, CRP and FC should be considered ancillary to endoscopic assessment.

Treatment options

One of the cornerstones of the management of refractory colitis is the minimisation of chronic steroid exposure. The choice of alternative treatment needs to be a balance between drug potency,

Table 1: Simple colitis activity index

Symptom	Score
Bowel frequency (day)	
1–3	0
4–6	1
7–9	2
>9	3
Bowel frequency (night)	
1–3	1
4–6	2
Urgency of defecation	
Hurry	1
Immediately	2
Incontinent	3
Blood in stool	
Trace	1
Occasionally frank	2
Usually frank	3
General well being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extracolonic manifestation*	1 per manifestation

*Arthritis, pyoderma gangrenosum, erythema nodosum, sclerosing cholangitis and uveitis.

(Remission \leq 3 points, significant change = 2 points)

side-effect profile, patient choice, age, sex, current medication and previous response to therapy, and the presence or absence of extra-intestinal symptoms. Prior to instituting novel immunosuppressant strategies it is important that standard first- and second-line treatments are optimised. Beyond this, second-line immunomodulators, biological agents and surgery might need to be considered.

Optimising treatment

Optimising 5 Aminosalicylates (5ASA)

5ASAs are commonly used in the treatment of UC. They are metabolised within the large bowel via various mechanisms and help in mucosal healing.

Two studies comparing low-dose (2.4 gram) and high-dose (4.8 gram) mesalazine therapy showed improved mucosal healing and remission rates with the higher dose strategy.^{7,8} Once daily dosing improves

adherence and is as effective as twice-daily dosing at inducing remission in mild to moderate active UC.⁹ In the presence of active disease, the dose of oral mesalazine should be maximised to at least 4 grams, preferably given once a day to improve adherence, as well as adding topical therapy in the form of mesalazine enemas 1 to 2 grams per day.¹⁰ Pentasa granules are available for those who find large 5ASA tablets difficult to swallow.¹¹

Optimising first-line immunomodulator

Thiopurines (Azathioprine and 6-mercaptopurine) should be considered first-line therapy for corticosteroid refractory or dependent disease. Thiopurines are metabolised by a complex multistep enzymatic pathway resulting in inhibition of lymphocyte proliferation.¹²

Their slow onset of action—these drugs can take 2 to 6 months to have their full effect¹³—precludes use as a single agent for

active disease. There are limited data on the use of thiopurines in ulcerative colitis, but a meta-analysis of 30 non-controlled studies and 7 controlled studies confirmed that thiopurines are more effective than placebo for the prevention of relapse in UC with a number needed to treat of 5, and absolute risk reduction of 23%.¹⁴

Thiopurines demonstrate wide inter-individual variability in terms of response, due their complex metabolism. Their metabolism is mainly regulated by Thiopurine S-methyltransferase activity (TPMT). Therefore checking TPMT activity prior to initiating thiopurine is recommended.¹⁵ The standard dose of azathioprine is up to 2.5 mg/kg/day and 6-mercaptopurine 0.75–1.5 mg/kg/day and dosage should be guided by TPMT activity.

Failure to respond to thiopurines can relate to non-adherence, inadequate dosing, or the preferential metabolism of the drug to the hepatotoxic metabolite 6-methyl-mercaptopurine (6-MMP), rather than the immunosuppressive metabolites, the 6-thioguanine nucleotides (6TGN). Monitoring of 6TGN and 6MMP levels may, therefore, be useful in maximising the effect of thiopurines. The target level for 6TGN is 235–450 pmol/8*10E8 RBC. The threshold of 6TGN level of 235 had a significantly greater therapeutic response ($p < 0.001$) in a prospective study of paediatric IBD patients.^{16–18} Since then, there have been several prospective studies reporting a correlation between 6TGN and clinical response with a therapeutic cut-off above 235 pmol/8*10E8 RBC.

Monitoring the metabolites can identify “shunting”, which is defined by a ratio of 6TGN:6MMP of $>20:1$. When shunting occurs, the addition of allopurinol 100 mg reverses the effect. The thiopurine dose must be reduced to 1/4–1/3 of the regular dose and 6TGN and 6MMP levels monitored to guide dosing. Levels are best performed approximately 4 weeks after any change in dose.¹⁹

Second-line Immunomodulator Therapies

Methotrexate

Methotrexate and its breakdown products inhibit several enzymes in the metabolic

pathway of folic acid. While the cytotoxic and antiproliferative effects of high-dose methotrexate are ascribed to inhibition of dihydrofolate reductase, with consequent inhibition of DNA, RNA, and protein synthesis, the anti-inflammatory and immunomodulatory actions of low doses are probably due to inhibition of other folate dependent enzymes. Long-term low-dose methotrexate may lead to accumulation of adenosine, a lymphotoxic, immunosuppressive, and anti-inflammatory autotoxin. Other effects include interleukin 1 (IL-1) receptor blockade, increased production of the regulatory cytokine IL-2, decreased production of soluble IL-2 receptors, IL-6, IL-8, leucotriene B4, and antibodies, and impairment of neutrophil chemotaxis.²⁰

Limited data exist for the use of methotrexate in UC. Benefit has been suggested in small, uncontrolled studies of patients with steroid dependent disease who failed to respond to, or were intolerant of, thiopurines. A previous randomised double-blind placebo controlled trial used the low dose of 12.5 mg of oral methotrexate weekly in 67 patients with UC. This showed no significant difference in the induction or maintenance of remission between the two groups.²¹ A Cochrane database systematic review then concluded there was insufficient evidence to support its use in UC.²² However, a recent randomised-controlled study, currently only available in abstract form, showed clinical benefit for steroid-dependent patients, using the higher dose of 25 mg weekly, given parenterally.²³ We conclude that Methotrexate 25 mg weekly should be considered and discussed with patients, particularly for those who are steroid dependent.

Tacrolimus

Tacrolimus is a calcineurin inhibitor that acts via a mechanism similar to cyclosporine by inhibiting T lymphocyte activation and also production of interleukin 2. Two randomised, double-blind, controlled trials demonstrated that tacrolimus is effective in induction of remission for steroid refractory, moderately active UC.^{24,25} Moreover, the dose of tacrolimus is an important determinant of induction and maintenance of remission. In a recent double-blind, randomised, controlled study of 60 patients with

resistant UC, there was better response when dosing was aimed at achieving higher tacrolimus trough level (10–15 ng/mL) compared to low trough level (5–10 ng/ml) and placebo.²⁵ One long term prospective study of 27 patients with refractory UC from Japan has shown a cumulative colectomy-free survival of 62.3% at 65 months.^{26,27} However, in the absence of larger, randomised, controlled trials with lengthy follow-up periods, tacrolimus cannot yet be considered standard second-line immunosuppression for UC. In addition, tacrolimus is currently only available in New Zealand via the Named Patient Pharmaceutical Assessment (NPPA) scheme.

Cyclosporin A

While there is extensive experience with the use of cyclosporin A in the setting of acute severe colitis,²⁸ no prospective data exists for its use in refractory colitis.

Anti TNF-alpha monoclonal antibodies (Infliximab and Adalimumab)

Infliximab

Tumour necrosis factor (TNF)- α is a proinflammatory cytokine with a central role in the pathogenesis of inflammatory bowel disease. Infliximab is a chimeric monoclonal antibody directed against TNF- α .

The ACT1 and ACT2 studies are the seminal studies that investigated the use of infliximab in UC.²⁹ They were large, randomised, placebo-controlled trials that evaluated the efficacy of infliximab for induction and maintenance of remission in more than 700 patients, with moderately active UC in the outpatient setting. ACT1 was a 364 patient study comparing infliximab 5 mg/kg, 10 mg/kg or placebo at 0, 2 and 6 weeks, then every 8 weeks for a year. The primary endpoint was clinical response or remission at week 8. Response rates were achieved in 37.2% in placebo group, 69.4% in the 5 mg/kg and 61.5 % in 10 mg/kg ($p < 0.001$). Remission rates at week 8 were 38.8% in the infliximab 5 mg/kg ($p < 0.001$), and 32% in infliximab 10 mg/kg group ($p = 0.002$) compared to 14.9% in placebo group.

Also, patients who received infliximab 5 mg/kg and 10 mg/kg had a 45% and 44% clinical response at week 54, compared to placebo 20% with $p < 0.001$ for both. Clinical remission rates at week 54 were 34.7% in the infliximab 5 mg/kg group and 34.4% ($p = 0.001$) in the infliximab 10 mg/kg ($p = 0.001$) dose group, compared to 16.5% for placebo.

ACT2 was almost identical, but included 364 patients with disease refractory to 5ASA alone—which was 26% of the population—with a 30-week follow-up. The response at week 8 was 29.3% in the placebo group, 64.5 % in the 5 mg/kg group and 69.2% in 10 mg/kg group, with a p -value of $p < 0.001$ for the comparison between both infliximab groups and placebo. Remission rates at week 8 were 33.9% ($p < 0.001$) in the infliximab 5 mg/kg, and 27.5% ($p < 0.001$) for the infliximab 10 mg/kg, compared to 5.7% in placebo group.

The long-term data arising from ACT1 and ACT2 were recently published. 229 of 484 infliximab treated patients from these trials entered the long-term extension for 3 years. Overall 70 (30.6%) patients discontinued infliximab infusions for adverse events (24 [10.5%]), lack of efficacy (11 [4.8%]), required colectomy (1 [0.4%]), or for other reasons (34 [14.8%]). The proportion of patients who maintained a physician's global assessment score indicative of no or mild disease (score=0 or 1) during the extension studies was 76.5% at extension week 0, and ranged between 90.0% and 94.3% through to extension week 52. The improvement in the inflammatory bowel disease questionnaire scores observed in the main studies was maintained. During the long-term extension, the safety profile was consistent with that of the main studies and no new or unexpected safety issues were identified.³⁰

Adalimumab

Adalimumab is a recombinant human monoclonal antibody directed against TNF- α . Currently in New Zealand, adalimumab is not funded for use in UC. The efficacy of adalimumab has been investigated in two placebo controlled trials, ULTRA1 and ULTRA2, conducted in patients with moderately to severely active UC despite oral corticosteroids and standard immunosuppressants. ULTRA 1 compared

adalimumab 160/80 mg and 80/40 mg to placebo for the induction of clinical remission after 8 weeks of treatment. At week 8, 18.5% in the adalimumab 160/80 group ($p=0.031$ vs placebo) and 10% in the adalimumab 80/40 group ($p=0.833$ vs placebo) were in remission, compared with 9.2% in placebo group. Serious adverse events occurred in 7.6%, 3.8% and 4.0% of patients in the placebo group, adalimumab 80/40 and adalimumab 160/80 respectively. There were two malignancies in the placebo group and none in Adalimumab groups.³¹

ULTRA2 was a study of 494 patients that looked into the induction and maintenance of disease using adalimumab 160/80/40 mg versus placebo in moderate to severe chronic active ulcerative colitis. Primary endpoints were remission at weeks 8 and 52. Overall rates of clinical remission at week 8 were 16.5% in the adalimumab group and 9.3% in the placebo group ($p=0.19$), corresponding values for week 52 were 17.3% and 8.5% ($p=0.04$). Serious adverse events occurred in 12% of patients given adalimumab or placebo. Serious infections occurred in 1.6% of patients given adalimumab and 1.9% given placebo.^{32, 33}

Combination therapy (Azathioprine and antiTNF- α)

The question as to whether standard immunosuppression should be used in combination with antiTNF- α therapy has not been well investigated. UC SUCCESS was a 16-week trial in biologic naïve patients with moderately severe UC.³⁴ Patients were failing corticosteroids and either naïve to azathioprine, or had stopped azathioprine more than 3 months before entry. Patients were randomised to infliximab, azathioprine or combination azathioprine and infliximab (induction and maintenance). The primary endpoint was steroid-free remission at week 16. Combination therapy with infliximab and azathioprine was found to be superior to both azathioprine and infliximab monotherapy in inducing remission in patients with moderately severe UC. Steroid-free remission at week 16 was achieved in 23.7% (18/76) of patients on azathioprine monotherapy, 22.1% (17/77) of patients given infliximab monotherapy and 39.7% (31/78) of patients given infliximab and azathioprine combi-

nation therapy ($p=0.032$ for combination vs azathioprine monotherapy and $p=0.017$ for combination vs infliximab monotherapy)

Access to antiTNF- α therapy for UC in New Zealand

In New Zealand, infliximab is now funded by PHARMAC and the current criteria for its use are all of the below:

- Patient has histologically confirmed ulcerative colitis; and
- The Simple Clinical Colitis Activity Index (SCCAI) ≥ 4 ; and
- Patient has tried but had inadequate response to or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximum-tolerated doses for an adequate duration (unless contraindicated) and corticosteroids; and
- Surgery (or further surgery) is considered clinically inappropriate; and
- Patient must be reassessed for continuation after 3 months

Surgery

Thirty percent of patients with ulcerative colitis will eventually come to proctocolectomy and this includes some with troublesome distal colitis. The decision as to whether to proceed to surgery is obviously a big one, with life-long consequences. The discussion about the possibility of surgery should be started early if a patient has troublesome disease. There are many aspects to be considered. Introducing the need for surgery late in the process is difficult for all. Care must be managed by a multidisciplinary team comprising the patient and their family, gastroenterologist, colorectal surgeon, stoma-therapist and other expertise as required. A clinical psychologist can be valuable, especially for younger patients.

Removing the colon and rectum in poorly controlled ulcerative colitis restores physical well-being and quality of life.³⁵ Long-term concerns about neoplasia are put aside. Patients are understandably very concerned about avoiding a “bag”. However the starting point of a discussion with the patient about surgery should focus on whether or not the time has come to remove

the colon and rectum. Although the patient will often have a strong preference for an ileal pouch, the type of reconstruction—ileal pouch or permanent ileostomy—should be a secondary consideration. The goal for most requiring proctocolectomy is an ileal pouch, but patients must accept that if they have complications they may require a permanent ileostomy. Long-term pouch failure rates are in the order of 5%.³⁶ Reassuringly, patients with either an ileal pouch or a permanent ileostomy typically have the same quality of life, matching that of the general population.^{37,38} However, quality of life is likely to be reduced if the patient is troubled by difficult chronic pouchitis (5%), or is a teenager or young adult with an ileostomy. For a typically functioning pouch, patients empty their pouch 4–8 times a day. Although this sounds frequent, patients don't have urgency and can usually defer for greater than 20 minutes. So, typical frequency is not a concern. Up to 30% may have a degree of minor leakage at night and 10% during the day.³⁹

Surgery provides a cure for the colitis, but carries a risk of a variety of short- and long-term complications. To reduce the risk of post operative complications, surgery is usually staged. Post-operative complications occur more frequently in patients who have been on greater than 20 mg of prednisone per day for 6 weeks or longer.^{40,41} Postoperative complications are not significantly increased with the use of thiopurines, calcineurin inhibitors or biological agents.^{42,43} Great care is needed with the occasional malnourished and immunosuppressed patient, where there may have been too much delay making treatment choices. If a patient is malnourished, septic, or on higher dose steroids, a colectomy, leaving the rectum, is usually the first operation to get the patient well. During later surgery a proctectomy is carried out, usually with the formation of an ileal pouch.

In the post-operative period, the most common serious problems from ileal pouch surgery are an anastomotic leak and subsequent pelvic abscess (5–10%). After creating an ileal pouch, it is usually covered with a temporary ileostomy to mitigate the effects of an anastomotic leak. The ileostomy is closed after about 3 months. Overall, there is a 30% chance of perioperative morbidity,

but the mortality rate in large series is very low.³⁶ Patients choosing a permanent ileostomy have a lower risk of perioperative complications and, particularly in older patients, this can be a factor in some patients' decision making.

Long-term complications of surgery need to be discussed with patients prior to surgery. There is about a 10% life-time risk of adhesive small bowel obstruction, which may require reoperation. In women who have not completed their family, if the rectum is removed there is probably a 20 to 30 percent reduction in fertility due to scarring in the pelvis.⁴⁴ Laparoscopic surgery is associated with less adhesions and may reduce infertility rates.⁴⁵ For these women, consideration can be given to an initial colectomy with end ileostomy and then waiting until child bearing is complete before later proctectomy and pouch formation. An ileorectal anastomosis is an option that may come up in discussion, but this is not favoured outside Scandinavia due to poor functional results and a high-rate of later proctectomy.

Thirty to 50% of patients will experience an episode of pouchitis. Acute pouchitis is usually episodic and settles quickly with antibiotics. The most common long-term problem with an ileal pouch is chronic pouchitis and this occurs in about 5%. Chronic pouchitis is managed with ongoing medical therapy, usually antibiotics, but in 1% may lead to pouch removal. If there is peri operative pelvic sepsis from an anastomotic leak, this can lead to a variety of chronic problems including fistulas, sinuses and strictures that can lead to poor function. Between 5 and 10% may also turn out to have Crohn's disease in the long-term, with problems of strictures or fistulas. Any of these problems can lead to further surgery, revision of the pouch or in some cases removal of the pouch and a permanent ileostomy.^{46,47} The outcomes of surgery are influenced by the experience of the surgeon and the volumes of colectomies being performed by the centre.⁴⁸

In summary, surgery is a major undertaking that is currently required in 30% of patients with ulcerative colitis. There is significant potential for morbidity, but overall greater than 90% of patients are pleased with their resulting health state and bowel function.³⁶

Appendicectomy

The inverse relationship between ulcerative colitis and appendicectomy has been investigated in epidemiological studies. A Swedish cohort study demonstrated that the protective effect of appendicectomy was restricted to appendicectomy performed under the age of 20 years for appendicitis or lymphadenitis, but not for non-specific abdominal pain without objective evidence of inflammation.⁴⁹ The theoretical explanation, based on T-cell population studies of resected appendixes, is that the appendix provides an inflammatory site and might play a role in the development of ulcerative colitis.⁵⁰

A recent meta-analysis regarding the effect of appendicectomy on ulcerative colitis activity compared five case-controlled and one cohort study, all with conflicting results.⁵¹ Due to the diversity of outcomes, insufficient adjustment for confounders and heterogeneous methodology, the pooled data were not comparable in this meta-analysis and no recommendation regarding any benefit of appendicectomy could be made. Currently, it is not possible to recommend appendicectomy for refractory ulcerative colitis, except in the setting of a clinical trial.

Biological treatments of proven benefit other than Anti TNF- α monoclonal antibodies

The treatments described in this section are neither freely available, nor funded in New Zealand at this time, but it is likely that some will become available in the future and many of these treatments (and other upcoming therapies) are available via clinical trials.

Other antiTNF- α therapies

Golimumab

Golimumab is a fully humanised anti-TNF α agent, which has been investigated in the treatment of moderately active UC and is administered in a 4 weekly subcutaneous injection. The use of golimumab was investigated in an integrated phase 2 dose-finding and phase 3 dose confirmation clinical trial of 1,064 patients with UC who were naïve to biological treatment and had failed immunomodulator, steroid and/or 5ASA therapy (774 pts in phase 3).⁵² Patients were randomised to

groups given golimumab doses of 100 mg and then 50mg (phase 2), 200 mg and then 100 mg, or 400 mg and then 200 mg 2 weeks apart. The phase 3 primary endpoint was clinical response at week 6. The secondary endpoint was clinical remission at week 6. The clinical response rates at week 6 were 51% and 54.9% among patients given 200 mg/100 mg and 400 mg/200 mg respectively, vs 30.3% among those given placebo (both $p < 0.0001$). Rates of clinical remission were significantly greater in both golimumab groups vs placebo ($p < 0.0014$). Golimumab was approved for the treatment of UC by the US Food and Drug Administration (FDA) in May, 2013, and also by the European Medicines Agency (EMA), but is currently not available in New Zealand.

Antibodies to adhesion molecules (integrins)

Vedolizumab

Vedolizumab is a monoclonal antibody that selectively blocks $\alpha 4\beta 7$ integrin expressed on lymphocytes. $\alpha 4\beta 7$ integrin is responsible for T-cell homing into gut-associated lymphoid tissues through its binding to mucosal addressin cell adhesion molecule (MAdCAM), which is present on high endothelial venules of mucosal lymphoid organs.

A phase III trial investigated the induction and maintenance efficacy of vedolizumab in 895 patients with moderate to severe treatment refractory UC. Induction treatment consisted of two infusions of 300 mg on day 1 and day 15. The clinical response rate at week 6 was significantly higher in the treatment arm compared to placebo (47.1% vs 25.5% $p < 0.0001$). A maintenance study revealed clinical remission rates at week 52 of 44.8% for 4 weekly treatments compared to 15.9% for placebo $p < 0.0001$.⁵³

Vedolizumab has been approved by FDA in 2014, and also in many European countries, for the management of moderate to severe UC.

Inhibitors to Janus Kinases

Tofacitinib

Tofacitinib is an oral inhibitor of Janus Kinases (JAK) 1, 2 and 3, resulting in

blocking of interleukin 2, 4, 7, 9, 15 and 21 pathways. Its use has been investigated in a double-blind placebo controlled phase II trial in 194 adults with moderate-severely active UC.⁵⁴ Patients were randomised to receive twice daily tofacitinib at doses 0.5, 3, 10 and 15 mg and placebo for 8 weeks. Clinical remission rates at 8 weeks of 48% and 41% of patients were seen at doses of 10 mg ($p < 0.001$) and 15 mg ($p < 0.001$) respectively compared to the placebo rate of 10%. No long-term data are available. A dose-dependent increase in both low- and high-density lipoprotein cholesterol was seen, which might restrict this agent's use in the future.

Other treatments of uncertain benefit

Leucocytapheresis

This technique involves removal of neutrophils, monocytes and lymphocytes via an extracorporeal system of either cellulose acetate beads or a polyester fibre filter. Each session lasts an hour, during which 2–3 litres of blood is drawn from one arm, filtered, and then returned to the other. A course of treatment takes up to 5–10 sessions at 1–2 weekly intervals.^{27,55} Its use has been investigated, mostly in Japan, with observational and randomised studies. In 2010, an attempt at metanalysis of the existing studies highlighted methodological concerns (lack of controls, small sample size and short duration follow-up).⁵⁶

One well-designed, randomised, double-blind, sham-controlled study comparing active leucocytapheresis to sham treatment did not show any significant benefit for the treatment of moderate to severe UC patients.⁵⁷ While leucocytapheresis is a relatively safe procedure, technical issues, such as the need for adequate venous access, the cost, and the lack of data would suggest it is not ready for widespread use.

Faecal microbiota transplantation (FMT)

Part of the pathogenesis of inflammatory bowel disease could be related to dysbiosis of the gut microbiota interacting with individual genetic predispositions via the mucosal immune system. One way of manipulating the gut microbiota is via faecal transplant. The process consists of the

transfer of gastrointestinal microbiota from a healthy donor, via intestinal installation of a liquid suspension, to restore the intestinal microbiota of a diseased individual.^{58,59}

A recent meta-analysis of the use of faecal transplantation in the treatment of inflammatory bowel disease included nine studies of FMT for maintenance or treatment of IBD, and eight related to the treatment of infectious diarrhoea in IBD.⁶⁰ It was not possible to conduct the meta-analysis due to the lack of randomised controlled trials, small number of reports and heterogeneity of protocols and outcomes. Of the 17 case series/reports of patients treated for IBD, the majority experienced reduction of symptoms (19/25), cessation of IBD medications (13/17) and disease remission (15/24). There was also resolution of *Clostridium difficile* infection in all those treated for this.

More recently, two randomised controlled studies of FMT for active UC in the absence of infection have given directly opposing results, with one showing no benefit of FMT over placebo, and the other showing clear benefit.^{61,62} An interesting finding in the positive study was that response related directly to the donor used. Seven of the nine patients in remission after FMT received fecal material from a single donor.⁶²

Thus, we conclude that currently there is some evidence that FMT might be a potential effective and safe treatment in UC, but that issues, such as the most advantageous microflora in the donor stool, need to be carefully considered before it can be recommended in routine practice.

Paediatric considerations

Many of the above issues and consideration are also relevant to children and adolescents with refractory UC. UC is typically more extensive in children than in adults, with the majority having pan-colonic involvement and only a small number having limited distal disease or proctitis.⁶³ Further, reports illustrate early extension of disease in those with limited involvement at diagnosis.

Active UC may impact adversely upon weight, linear growth and pubertal development in children.⁶⁴ Consequently, important aspects of monitoring children and adolescents with UC include: serial

measurements of weight and height; assessment of pubertal status (in adolescents); along with symptom review and consideration of the impact of the disease upon daily activities (eg, school, sporting and social activities).

Disease activity in children with UC can be assessed by the use of the Pediatric UC disease index (PUCADI), a well-validated composite score, ranging from 0 to 85, with a score of <10 indicating remission.⁶⁵

In terms of standard drug therapies, corticosteroid have further particular concerns in paediatric populations with UC.⁶⁶ The common short-term side effects of steroids (such as moon facies and increased acne) are poorly accepted, especially by adolescents. Furthermore, other concerns of ongoing steroid exposure or repeated courses of CS include suppression of linear growth and impaired development of bone strength. Consequently, CS dependence or resistance should be tolerated even less in children with UC than in adults.

5-ASA drugs have equally important roles in children as described above for adults with UC. Although numerous studies support the early introduction of thiopurines in moderate to severe Crohn's disease, there is less data in UC. However, most practitioners would consider this approach, especially in a child requiring CS to induce remission or in those with refractory disease.⁶⁷ Further, paediatric data provide some support for tacrolimus, with less for biologic drugs at present.

Surgical intervention may have further particular considerations in children and adolescents.⁶⁵ Firstly, colectomy should be

considered with and following extensive discussion with a paediatric surgeon experienced in this procedure in young children. Close collaboration with adult colorectal surgeons will also be required. Secondly, the timing of colectomy will also need careful consideration. One important factor, for example, is the potential adverse impacts of pelvic surgery upon future fertility in young girls.

Overall, the management of refractory UC in children and adolescents requires a broad multi-disciplinary approach, with consideration of the impact of the disease and timely introduction of appropriate therapies.

Conclusions

If optimisation of standard immunosuppression fails in mild to moderate UC, then the main therapeutic options currently available are antiTNF- α therapy and colectomy. While other immunosuppressive strategies exist, they have not been demonstrated to have the same efficacy as antiTNF- α therapy. Currently the evidence for methotrexate is limited and, while there is some evidence for tacrolimus, the available studies are small.

In deciding the next therapeutic step in colitis which is refractory to standard immunosuppressive therapy, a multidisciplinary approach is essential. Discussion of what surgery involves with a colorectal surgeon and stoma-therapist will greatly aid decision making and should be endeavoured early in the process. In many cases a trial of antiTNF- α therapy will be warranted but in some situations proceeding straight to surgery may be appropriate.

Competing interests:

Stephen J Inns reports personal fees and other from Abbvie Paediatric Advisory Board and Janssen Advisory Board outside the submitted work; Andrew S Day reports other from Janssen Advisory Board and Abbvie Paediatric Advisory Board outside the submitted work.

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