

A practical approach to positioning therapies in ulcerative colitis

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Abstract

The therapeutic landscape of ulcerative colitis (UC) has undergone significant change over the last 2 decades. While there are multiple new therapies for the management of UC, long-term remission rates remain low, and this may be in part due to the difficulty of navigating a successful treatment strategy. In this review, we propose a rational framework for treatment selection, sequencing, and optimization in patients with UC. We outline treatment goals and targets for UC, followed by a discussion of the challenges in treatment selection and considerations to help guide a sequencing strategy. These include an assessment of a therapy's efficacy and safety, the convenience in the delivery of the therapy, ease of access, and patient-related factors. We then provide an overview of the currently approved therapies for UC, with an in-depth analysis of their advantages and disadvantages. Finally, we conclude with future directions in the management of UC, which include the use of naturopathic therapies, faecal microbiota therapy, the use of precision medicine, and other strategies such as combination therapy.

Key words: ulcerative colitis; inflammatory bowel disease; treatment sequencing.

Introduction

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by chronic inflammation of the colon and rectum.¹ It affects approximately 1.5 million individuals in North America, with an estimated annual incidence of 15 cases per 100 000 people.² Over the past 2 decades, the therapeutic landscape for UC has undergone significant evolution, with the approval of several new agents targeting diverse inflammatory pathways.³ Despite these advancements, only 20%–30% of patients achieve remission after initial treatment, and fewer than half of these patients maintain remission over time.⁴ The challenge of achieving long-term disease control underscores the importance of selecting an optimal treatment strategy for patients with UC. In this review, we propose a rational framework for treatment selection, sequencing, and optimization in patients with UC.

Treatment goals in UC

Although there is no medical cure for UC, treatment goals focus on controlling the disease and improving patient outcomes. Key objectives include early diagnosis, improvement in quality of life, and induction of both clinical and endoscopic remission. Additional goals include preventing relapses, disease progression, and complications, all within an affordable and accessible healthcare setting. Further, it is important to recognize that a patient's goals may look different than a clinician's. In a recent international survey, most patients with IBD defined remission primarily as a resolution of IBD symptoms (45%), followed by the ability to de-escalate

treatment (25%), normalized test results (19%), or no longer needing treatment (10%).⁵ In contrast, clinicians most commonly defined remission by normalized test results (70%), followed by resolution of symptoms (23%), no longer needing treatment (4%), or ability to de-escalate treatment (3%). Furthermore, patients generally expected longer durations of disease control than physicians.⁵ These discrepancies demonstrate the importance of regular and clear communication between patients and healthcare teams to align treatment goals and ensure successful care.

Considerations to help guide sequencing in UC

Given the multiple options available for UC, navigating a treatment strategy can be challenging. This complexity is heightened by the heterogeneity of disease presentation and the varying patterns of loss of response to therapy (ie, primary vs secondary loss of response and immune vs non-immune mediated). There are also challenges in the interpretation of available clinical trial data due to differences in clinical trial designs and inclusion criteria among therapies. This is particularly difficult for trials of second-line (2L) treatments for UC, which inherently have a selection bias of more difficult-to-treat disease. Interpreting results from the 2L trials and trials containing patients who have been on multiple prior lines of therapy is challenging, as it is difficult to separate biological resistance from the mechanism of the drug vs a more complicated progressive disease of patients who have already failed initial therapy.

Given the many treatments available for the management of UC, consideration should be given to the optimal first-line (1L) treatment, when and how to position subsequent therapies, and when to decide on surgical management. Decision making should balance several aspects, including efficacy, safety, convenience, drug access, and patient-related factors.

First, patient factors should be used to categorize patients as low or high risk for colectomy, which will impact the choice of treatment. This starts with an assessment of how sick the patient is based on symptoms, inflammatory markers, and acuity of illness. Then, prognostic factors should separate patients into those who are low risk for colectomy and those who are high risk. Low-risk factors include a limited anatomic extent and mild endoscopic disease while high-risk factors include extensive colitis, deep ulcers, age of diagnosis less than 40 years old, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate, steroid-requiring disease, history of hospitalization, *Clostridium difficile* infection, and cytomegalovirus infection.^{6,7}

In terms of efficacy, the treating clinician should evaluate available evidence supporting the use of each therapy, including clinical trial and real-world data, and differences in outcomes for biologic-exposed vs. biologic-naïve patients. Drug safety profiles must be considered, including drug-adverse events, disease-related adverse events, and the severity of the patient's disease in establishing a risk-benefit assessment. The choice of therapy will also be affected by relative and absolute contraindications as relevant to the patient. The mode of delivery and frequency of dosing are relevant to the convenience of delivering the therapy and may influence patient preference towards a particular therapy. Drug access including insurance coverage and the cost and time to the patient can ultimately determine the selected therapy. Lastly, patient factors to consider in the selection of therapy include the disease phenotype, comorbidities, and co-existing extraintestinal manifestations (EIM) of IBD that may be concurrently targeted by the same therapy. In summary, an individualized approach, balancing the examined features can facilitate an ideal treatment selection and sequencing strategy.

Clinical pearls for induction of remission

The first goal of initiating treatment is to induce remission, and this should be based on identified targets of treatment.⁸ Remission should be divided into symptomatic remission, which includes normalization of stool frequency and cessation of rectal bleeding. Next, disease control should be achieved, which includes endoscopic healing (Mayo Endoscopic Score of 0 or 1) or other surrogates of inflammation of the mucosa (faecal calprotectin or CRP).⁹ Evolving targets to assess treatment include resolution of bowel urgency, use of intestinal ultrasound, and achieving histological remission.⁸⁻¹⁰ Another consideration is whether response to treatment can be assessed objectively at earlier timepoints such as at 6 weeks after initiating therapy.¹¹ Indeed, several studies have demonstrated early objective testing with faecal calprotectin and intestinal ultrasound are associated with improved outcomes.¹²⁻¹⁴

For induction of remission, the choice of the 1L therapy should be guided by disease location, disease activity, and prognosis. We propose these clinical pearls for the induction phase in the management of UC: (1) It is important

to remember not to make patients “earn” the appropriate therapy by failing other treatments first; (2) Do not accept less than stable and objective disease control (ie, remission) before moving onto the maintenance phase of management; and (3) It is also important to consider EIMs that can be concomitantly treated.

While the use of corticosteroids for UC has been recognized as a breakthrough discovery in management in the 1950s, it is well recognized that steroids are associated with the worst clinical outcomes, and the need for corticosteroids for disease control is associated with a known prognosis of colectomy. Therefore, the standard approach to the management of UC includes avoidance of steroids when possible, and when they are used, the embrace of a steroid-sparing strategy for ongoing maintenance. To these ends: (1) Consider a one-and-done approach to steroids. Steroid avoidance should be emphasized when possible and patients should be spared from long-term steroid use, particularly as newer therapies may not require steroids for bridging^{15,16}; (2) remember that the need for steroids is a prognostic marker of UC severity¹⁷; (3) In patients with mild to moderately active UC, an emphasis should be made on using non-systemic steroids (topical or budesonide preparations) first to reduce the systemic side effects of steroids¹⁸; (4) vitamin D and calcium supplementation should be considered when prescribing steroids given their detrimental effects on bone mineral density¹⁸⁻²¹; (5) The optimal steroid tapering strategy is unknown, and in general, steroid tapers in UC are much longer than are necessary; the tapering schedule should be timed to the successful induction of the maintenance or other inductive strategy; any steroid course less than 2 weeks does not require a taper and long steroid tapers in this scenario may be avoided altogether.²²

Therapies for UC

Conventional therapies for UC

5-Aminosalicylic acid

5-Aminosalicylic acid (5-ASA) therapies are effective for induction of mild to moderately active UC in 15%-40% of patients and effective for maintenance of mild to moderately active UC in 57%-78% of patients.²³⁻²⁵ The success of 5-ASA relies on reaching the location of the disease, and therefore, it is important to understand the mechanism of delivery (ie, moisture delivery vs pH vs topical).²⁶ Combined oral and rectal 5-ASA therapy has been demonstrated to be more effective than either alone.²⁷

While 5-ASA is generally well-tolerated, rare side effects include 5-ASA intolerance and interstitial nephritis, which necessitates routine monitoring of renal function.²⁸⁻³¹ While effective for some patients with UC, its long-term benefits may be limited. Roughly 37% of patients receiving 5-ASA maintenance therapy relapse within 6-12 months.² Further, even in patients who achieve remission, bothersome symptoms such as fatigue often persist, limiting patient quality of life.³² If escalation to more advanced therapies is required, the continued use of 5-ASA does not appear to modify outcomes and is thus not a cost-effective strategy.^{33,34}

Advanced therapies

Advanced therapies for UC include monoclonal antibodies and targeted synthetic small molecules. Monoclonal antibodies for UC include anti-tumor necrosis factor (TNF)

agents (adalimumab, golimumab, and infliximab), anti-integrin inhibitors (vedolizumab) and anti-interleukins (IL) (the IL-12/23 p40 inhibitor, ustekinumab, and the IL-23 p19 inhibitors guselkumab, mirikizumab, and risankizumab). Small molecules approved for the induction and maintenance of UC include the Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib), and sphingosine-1-phosphate receptor (S1PR) modulators (etrasimod and ozanimod). These therapies are considered for patients with moderately to severely active UC, patients who do not respond to 5-ASA, are steroid-dependent, or otherwise have a poor disease prognosis.

There is a paucity of head-to-head trials and real-world studies comparing advanced therapies for the management of UC.^{35,36} Therefore, assessments have been made through network meta-analyses. One network meta-analysis evaluated 23 trials involving advanced therapies for induction and maintenance of moderately to severely active UC (but did not include guselkumab, mirikizumab, risankizumab, or etrasimod) and found that upadacitinib was the most efficacious induction therapy and this was independent of prior biologic exposure.³⁷ The analysis also found no difference in serious adverse events or serious infections across all therapies.³⁸

There has not been a pragmatic sequencing trial in UC, so decisions related to which therapies to use in which patients are left for inference from the trials, extra-intestinal manifestations, and other factors. In the following section, we review the current advanced therapies approved for the management of UC. A summary of our suggestions for choosing therapies in UC by disease severity and co-existing EIMs is in Tables 1 and 2. There are also relative and some absolute contraindications of our therapies, and these are included in Table 3. Tailoring the treatment based on all these factors will determine the appropriate treatment option for the individual patient.

Biologics

Anti-TNF. Anti-TNF agents for UC include adalimumab, golimumab, and infliximab. They were the first biologics approved for UC and are the most used biologics.⁵⁶ Both intravenous and subcutaneous options for infliximab are now available for maintenance therapy of moderate to severely active UC, as a subcutaneous compound was demonstrated to be effective for maintenance after IV induction in the LIBERTY-UC trial.⁵⁷ Benefits include rapid onset, and

Table 1. Sequencing treatment strategies based on disease severity and efficacy.

Disease severity	Treatment*
Mildly to moderately active UC	5-ASA optimization
Moderately to severely active UC after 5-ASA	Consider S1PR modulator before other advanced therapies
Moderately to severely active UC (otherwise)	First line Vedolizumab > adalimumab Vedolizumab ~ infliximab Other options: JAK inhibitors, IL-12/23, and IL-23 therapies Second line JAK inhibitor after anti-TNF Anti-TNF > vedolizumab

*Consider induction with systemic or topical corticosteroids.

concomitant treatment of rheumatologic and dermatologic EIMs including enteropathic arthropathy, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, sacroiliitis, and plaque psoriasis.⁵⁸ Safety considerations include reactivation of latent tuberculosis, chronic hepatitis B, and paradoxical immune reactions of the joints and skin.⁵⁶

Combination therapy of infliximab with azathioprine (or weekly methotrexate) is more effective than infliximab monotherapy and this is likely true, although unproven, for the other anti-TNFs.⁵⁹ Concomitant therapy may decrease the risk of immunogenicity (ie, developing antibodies to biologic therapy) and infusion reactions.^{60,61} They are the only class of therapy that has data and support for therapeutic drug monitoring and proactive serum concentration of the drug should be considered during the loading phase in patients who are at high risk for not responding (ie, hypoalbuminemia or obese).^{62,63} The optimal dosing strategy for induction in acute severe UC remains unclear and was investigated in the PREDICT-UC trial, an open-label multicentre randomized controlled trial (RCT) that compared intensified and standard infliximab rescue strategies in patients with acute severe UC.⁶⁴ The study did not find a significant difference in their primary outcome, defined as clinical response at day 7, between patients randomized to 10 mg/kg vs 5 mg/kg at day 0. However, post-hoc analysis did reveal a greater clinical response in patients with low albumin and high CRP who received 10 mg/kg as the index dose vs the 5 mg/kg group, though this was not statistically significant. The authors also did not find any significant difference in various secondary endpoints, such as time to clinical response, change in CRP level from baseline to day 7, clinical outcomes at 3 months, and adverse events. It should be noted that the study was limited to an open-label design, and that serum infliximab drug level and faecal calprotectin levels were not assessed.

Table 2. Clinical scenarios and co-existing conditions that can be concomitantly treated by a given therapy in UC.

Clinical Scenario/co-existing condition	Therapy consideration
Enteropathic arthropathy	Sulfasalazine ³⁹ Methotrexate ⁴⁰ Anti-TNF ⁴¹ JAK inhibitor ⁴¹
Psoriatic arthritis (peripheral spondyloarthropathy)	Methotrexate ⁴² Anti-TNF ⁴³ JAK inhibitor ⁴⁴ Anti-IL-23 therapies ⁴⁵
Rheumatoid arthritis	Methotrexate ⁴⁶ Anti-TNF ⁴⁷ JAK inhibitor ⁴⁸
Axial spondyloarthropathy (ankylosing spondylitis and sacroiliitis)	Anti-TNF ⁴¹ JAK inhibitor ⁴¹
Plaque psoriasis	Methotrexate ⁴⁹ Anti-TNF ⁵⁰ Anti-IL-23 therapies ⁵¹
TNF-induced palmar plantar pustulosis	Non-anti-TNF therapies ⁵² Favour IL-23 ⁵²
Alopecia	JAK inhibitor ⁵³
Multiple sclerosis	Ozanimod ⁵⁴ Possibly etrasimod ⁵⁵

Table 3. Clinical scenarios and contraindications that may influence a choice of therapy.

Clinical scenario/ contraindicating treatment	Treatment with relative or absolute contraindication	Comment
Latent tuberculosis	Anti-TNF	Can treat for tuberculosis and start anti-TNF
Chronic hepatitis B	Anti-TNF Anti-IL-23 therapies	Monitor quantitative Hepatitis B viral load
Melanoma	Anti-TNF	Remember dermatologic screening for patients on advanced therapies and small molecules
Anti-drug antibodies to first anti-TNF	Anti-TNF	Protect against antibodies with next anti-TNF with combined immunomodulator and drug monitoring. Consider non-anti-TNF options
Uveitis, macular oedema	S1PR modulators	Relative contraindication—share management and discussion with ophthalmology. Macular edema is reversible
Type 2 heart block	S1PR modulator	Not contraindicated in Type 1 heart block or pacemaker or coronary artery disease/congestive heart failure
Personal history or first-degree relative with lymphoma	Anti-TNF thiopurine	Vedolizumab and anti-IL-23 appear reasonable options
Smokers, > 65 years old, other cardiovascular or coronary artery disease risks	JAK inhibitors	Note that major adverse cardiovascular events and venous thromboembolism have not been seen in the IBD population
Cytotoxic chemotherapy for cancer	Immunosuppressive treatments	Expect rebound in IBD after chemotherapy stops and when marrow recovers

Anti-integrin. Vedolizumab is a gut-selective antibody against the $\alpha 4\beta 7$ integrin and is a safe and efficacious therapy for moderate to severely active UC.⁶⁵ The VARSITY trial is the only head-to-head trial of advanced therapy in UC. It demonstrated the superiority of vedolizumab to adalimumab in achieving clinical remission and mucosal healing in patients with moderate to severely active UC.³⁵ However, a caveat to this finding is that when the investigators stratified patients by those who were anti-TNF naïve and anti-TNF exposed, vedolizumab was only significantly superior to adalimumab for anti-TNF naïve patients. Comparisons of vedolizumab to other therapies have also been made in real-world studies. The EVOLVE study was a retrospective chart review of patients with UC and Crohn's disease (CD) treated with vedolizumab or anti-TNF in Canada, Greece, and the United States.⁶⁶ The review included 604 patients with UC and found that the rates of clinical remission and mucosal healing were similar between vedolizumab and anti-TNF agents, but rates of serious adverse events and serious infections were significantly lower in patients treated with vedolizumab.⁶⁶ Another multi-centre European real-world study compared tofacitinib

to vedolizumab in patients with UC with previous prior exposure to anti-TNF therapy.⁶⁷ There was no significant difference observed in achieving corticosteroid-free clinical remission at week 16 though endoscopic improvement and histological healing were higher in patients treated with tofacitinib.⁶⁷ **Anti-IL23/23 and IL-23.** The IL-12/23 p40 (ustekinumab) and IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) are also considered efficacious for the management of UC.^{2,68-71} The main difference in their mechanism may be explained by their molecular targets.⁷² IL-12/23 inhibitors target the p40 subunit, a shared subunit between IL-12 and IL-23. In contrast, the IL-23 inhibitors target p19, a subunit in IL-23 only.⁷² Ustekinumab, guselkumab, and risankizumab are also approved for moderate to severe plaque psoriasis and active psoriatic arthritis, while mirikizumab is not.⁵¹ IL-12/23 and IL-23 inhibitors have an excellent safety profile. Though they can worsen chronic hepatitis B, they do not appear to increase the risk of reactivation of chronic tuberculosis.⁷³⁻⁷⁵ Cycling between IL-12/23 to IL-23 is likely also appropriate based on Crohn's and psoriasis experience.⁷⁶⁻⁷⁸

Small molecules

The small molecules, including JAK inhibitors (tofacitinib, upadacitinib) and S1PR modulators (etrasimod, ozanimod), offer benefits including the convenience of delivery as oral agents, avoiding monoclonal antibody challenges such as the protein leakage challenge of the inflamed bowel.^{79,80}

JAK inhibitors. Tofacitinib and upadacitinib have been shown to be effective therapies for moderate to severely active UC.^{38,81} JAK inhibitors are fast acting and effective for IBD-associated arthropathies including enteropathic arthropathy, and also have demonstrated efficacy for the treatment of psoriatic arthritis, rheumatoid arthritis, and the axial spondyloarthropathies.⁸² They are also beneficial for alopecia areata.⁵³ Cycling within class also appears to be effective for both JAK inhibitors based on 2 real-world studies.^{83,84} Adverse effects include increased lipids and increased risk of shingles (vaccination for herpes zoster is recommended).⁸² Relative contraindications include advanced age (older than 65 years old), smoking history, and prior venous thromboembolism and coronary artery disease though it is acceptable to use if there is concurrent treatment for these conditions.⁸⁵ There is insufficient evidence to support the use of JAK inhibitors in pregnant or nursing women. These therapies are rapidly effective and can therefore be used without corticosteroid induction. In addition, there is emerging evidence to support their use for acute severe ulcerative colitis in hospitalized patients with acute severe UC.⁸⁶⁻⁸⁸

S1PR modulators. S1PR modulators are small molecule therapies that target the receptors related to the signalling molecules and function by preventing the egress of activated lymphocytes from lymph nodes.⁸⁹ Post-hoc analyses demonstrate better efficacy in biologic-naïve patients and therefore it has been suggested that these therapies are appropriate to consider after 5-ASA therapy. In terms of safety considerations, there is an expected reduction in circulating lymphocytes but no increase in the risk of infections. Ozanimod has been associated with transient liver enzyme elevation in some patients. Because S1P is also involved in cardiac conduction, S1PR modulators are contraindicated in patients with second-degree heart block. Similar to the JAK inhibitors, these therapies have insufficient evidence for their use in pregnant or nursing

women.^{89,90} Benefits for most extra-intestinal manifestations remain generally unknown, though ozanimod is also approved for the treatment of multiple sclerosis.⁵⁴

Treatment monitoring

Once a therapy has been selected, it is critical to regularly assess the response to therapy using a pragmatic treat-to-target approach.⁹¹ We propose that after 6-12 weeks of choosing an initial therapy, a re-assessment of disease activity by targets and goals as previously outlined should be performed. Objective targets may include normalization of inflammatory markers including faecal calprotectin and CRP, improved colitis on imaging, and/or endoscopic improvement.^{11,92,93} In accordance with the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II recommendations, short-term targets should include symptomatic response and normalization of CRP, followed by intermediate targets of acceptable faecal calprotectin levels, and ultimately, long-term targets of endoscopic healing, normalized quality of life, and absent disability.¹¹ If the target has been reached, clinical follow-up is recommended in 6-12 months, with ongoing assessment of disease stability. If the targets have not been reached, the options include reassessment after more time has passed, dose adjustment of existing therapy, the addition of a second therapy, or wholesale swapping to a different treatment mechanism or surgery. A fundamental part of the treat-to-target approach to management includes discussion with the patient and shared decision-making.⁹¹

Future directions

There remains a large treatment gap in UC. As many patients are not able to achieve or sustain remission, it is important to continue advances in the management of UC, including the development of novel approaches such as new classes of medications outside of advanced therapies. In the following section, we review future directions for the management of UC, including naturopathic therapy, faecal microbiota therapy (FMT), precision medicine, and combined advanced targeted therapy. Additional novel strategies that have gained interest also include bridging therapies, tandem therapies, pulse therapy, and biomarker-driven options.

Naturopathic treatments for UC

Alternative or naturopathic therapies carry a significant interest in the population with IBD.^{94,95} Two naturopathies studied for the management of UC include curcumin and indigo naturalis (Qing Dai), which have been shown to have anti-inflammatory properties in colitis in animal models.⁹⁶ Curcumin is an active polyphenol extracted from the rhizomes of *Curcuma longa* L. from the ginger family *Zingiberaceae*.⁹⁷ A systematic review and meta-analysis involving 6 RCTs with a total of 385 participants with UC found that adjuvant curcumin was effective in inducing clinical remission but not in achieving clinical improvement, endoscopic remission, or endoscopic improvement.⁹⁸ There were no serious adverse events noted. Qing Dai consists of indigo naturalis, which is a dried powder derived from various plants.⁹⁹ A systematic review and meta-analysis that included 9 studies and a total of 299 patients with IBD (275 patients with UC) treated with adjuvant indigo naturalis found that it was associated with clinical remission and clinical

response, as well as endoscopic and histological response when reported.¹⁰⁰ One patient developed pulmonary hypertension, a reported adverse event of indigo naturalis, which was reversed upon treatment cessation.¹⁰⁰

A recent randomized double-blind study in Israel and Greece evaluated a combination herbal therapy of curcumin and indigo naturalis (CurQD) in patients with active UC.⁹⁶ The authors found that the co-primary outcome (clinical response combined with endoscopic or biomarker response) at 8 weeks was met in 43% of patients using CurQD compared to 8% in the placebo group ($P = .033$). The onset of CurQD effects was rapid, with clinical response apparent by day 16 and significantly faster compared to placebo patients who had a clinical response.

Faecal microbiota therapy

FMT involves the administration of healthy donor whole stool into the gastrointestinal tract of an individual.¹⁰¹ It is postulated that FMT may serve to correct gut microbiome dysbiosis that may be driving UC disease activity.¹⁰¹ While first used for UC in 1989, FMT has gained interest in the last decade as a potential strategy for the management of UC.^{101,102} A 2018 Cochrane review evaluated 4 studies with a total of 277 patients with UC.¹⁰³ Combined results suggested that FMT significantly increased rates of clinical remission by 2-fold in patients with UC compared to controls. Three of the studies had investigated endoscopic remission at 8 weeks, which was also found to be significantly greater in FMT compared to controls. A more recent systematic review and meta-analysis was conducted that included 6 double-blind RCTs with 324 patients with UC who received FMT.¹⁰⁴ Compared to placebo, FMT was associated with significantly increased combined clinical and endoscopic remission. The authors also did not find any significant difference between pooled or single stool donors, fresh or frozen FMT, and different routes or frequencies of delivery. Notably, the studies included are heterogenous in nature and patients had predominantly mild to moderate UC activity. While FMT is a promising therapy for UC, it should be emphasized that no guidelines currently recommend its use for UC except in the context of clinical trials.^{105,106} Further research is required to determine its place in treatment sequencing, its use for severe disease, and other characteristics of FMT treatment such as the route of administration (upper vs. lower gastrointestinal tract), the type of donor (single vs. pooled, preparation of stool, duration of therapy), and type of use (induction vs. maintenance, monotherapy vs. combination therapy strategy).^{105,106}

Precision medicine

Other novel strategies include novel mechanisms targeting other processes in UC using predictive genetic-based tools. The ARTEMIS-UC study was a phase 2 double-blind RCT that randomized patients with moderate to severely active UC to tulsikobart, an anti-TNF-like cytokine 1a (TL1A) compared with placebo.¹⁰⁷ Both TL1A and its receptor DR3 are implicated in the pro-inflammatory and fibrotic processes of IBD.¹⁰⁷ The study incorporated a genetic-based diagnostic test to identify if patients were more likely to respond to anti-TL1A. The authors found that a significantly greater proportion of patients who received TL1A achieved clinical remission and mucosal healing by week 12. However, the study did not find evidence that patients with a favourable genetic profile to respond to anti-TL1A therapy were more likely to benefit. The authors attributed this observation to the limited sample size analyzed.¹⁰⁷

Combined advanced targeted therapy

Many patients with UC have severe disease that is refractory to multiple agents. This has led to the increasing use of multiple concomitant advanced therapies.¹⁰⁸ Most data supporting combined advanced therapies stems from observational data.¹⁰⁹ The VEGA study was a randomized double-blind study that took place in 9 countries, whereby 214 patients with moderate to severely active UC were randomized to receiving combination therapy with golimumab and guselkumab, golimumab monotherapy, or guselkumab monotherapy.¹¹⁰ At week 12, patients in the combination therapy group achieved a significantly greater clinical response compared to the golimumab monotherapy but not compared to the guselkumab monotherapy group. Similarly, combination therapy achieved significantly greater endoscopic remission compared to both monotherapy options at week 12.¹¹⁰ While an encouraging option for UC, there remain several barriers. This includes the optimal strategy for combination treatments, the costs of multiple advanced therapies, the current limited understanding of risk stratification, and the type of patient who would benefit from combination therapy.¹⁰⁹

Summary

Selection of a therapy in UC is challenging, with various factors to consider, and advantages and disadvantages to each treatment option. Individualizing an approach by understanding the patient characteristics and then balancing efficacy, safety, tolerability, and access is critical in defining a sequence strategy for a patient. We propose a pragmatic treat-to-target approach to guide therapy while aligning patient goals to ensure optimal care. As the understanding of UC pathophysiology continues to advance, the future holds promise for more personalized and effective therapies. Continued research into novel treatments, biomarkers, and precision medicine approaches will likely lead to further improvements in an optimal sequencing strategy for the management of UC.

Author contributions

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Data availability

There are no data associated with this manuscript

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