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Review

Choosing Therapies in Ulcerative Colitis

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Abstract

Those managing ulcerative colitis (UC) must be aware of new treatments. Mesalamine (5-ASA) is the first treatment for mild UC. Steroids have been the first therapy for patients with more severe UC but these are not effective or safe long term. This means that other medicines are needed. Newer advanced therapies are now frequently used. There are several types of advanced therapies. These are the anti-TNF, anti-integrin and anti-IL12/23 agents as well as the JAK inhibitors and sphingosine1-phosphate receptor modulators. All of these are effective in treating UC. Choosing among treatments is complicated. There are multiple factors to think about when choosing a treatment for UC. Without research studies that directly compare the different treatments, the use of any one treatment should be based on effectiveness and safety. Other considerations include specific disease features, patient factors and the preference of patients.

Introduction

Ulcerative colitis (UC) is a chronic, relapsing, and remitting inflammatory bowel disease (IBD) subtype affecting the rectum and colon.[1] There are millions of IBD sufferers worldwide, with an increasing incidence worldwide.[1-4] Active mucosal inflammation in UC results in diarrhoea, rectal bleeding, systemic effects, and in a minority can cause life-threatening sequelae.[5-7] The recognition of the associated individual and societal health burdens has led to an increase in novel therapy development and availability.[8,9] The increasing number, mechanisms of action, variable efficacy, and overall complexity of therapies means that any physician managing UC requires a nuanced understanding of therapeutic application. This text is intended as an evidence-based guide for UC management, with a particular emphasis of advanced therapy utilization in moderate to severe UC.

The ideal therapy should be safe, efficacious, cheap, and have no harmful side effects. No agent has all these characteristics, meaning that a hierarchical approach to therapeutic positioning of available agents is needed with strong emphasis on individual patient and disease characteristics and patient preferences.

Treatment of UC

First-line therapy

The goal of therapy is to induce and maintain remission, while minimizing the need for corticosteroids. Following induction, maintenance of remission is maximized with continued medical therapy.[10] Goals of therapy have been evolving recently with the recognition that short-, medium-, and long-term goals may differ and that clinical remission in the absence of endoscopic healing and possibly even histologic remission may not be optimal for long-term outcomes.[11]

Ulcerative proctitis

Ulcerative proctitis should be initially managed with rectal 5-aminosalicylic acid (5-ASA) only. For those not responding to topical 5-ASA, rectally administered steroid therapy can be tried and for those individuals resistant to both topical 5-ASA and steroids other topical therapies such as tacrolimus or short chain fatty acids have been reported to be variably effective. It is unusual for a patient with proctitis to require systemic therapy, and most studies of systemic therapies have specifically excluded patients with proctitis.

Mild-to-moderate UC

Despite the availability of advanced therapies, 5-ASA-based therapies continue to be the first-line therapy for most patients with mild to moderate UC given the good efficacy and excellent safety profile.[10] Combination of oral controlled release 5-ASA with rectal administered 5-ASA may provide enhanced clinical response.[10] If response or remission is achieved, the same therapy should be continued as maintenance, though rectal preparations may not be preferred by patients for long-term treatment, and oral 5-ASA preparations can be utilized alone (Fig. 1).

In mild-to-moderate UC of any extent, oral multi-matrix (MMX) budesonide is also efficacious as an induction agent but has not been demonstrated to be an effective or safe maintenance therapy and, therefore, must be followed with another therapy that is effective for maintenance of remission. This may be a 5-ASA preparation but, as discussed further, may require a thiopurine or advanced therapy to maintain remission when a patient has required steroid therapy to achieve remission.[12,13]

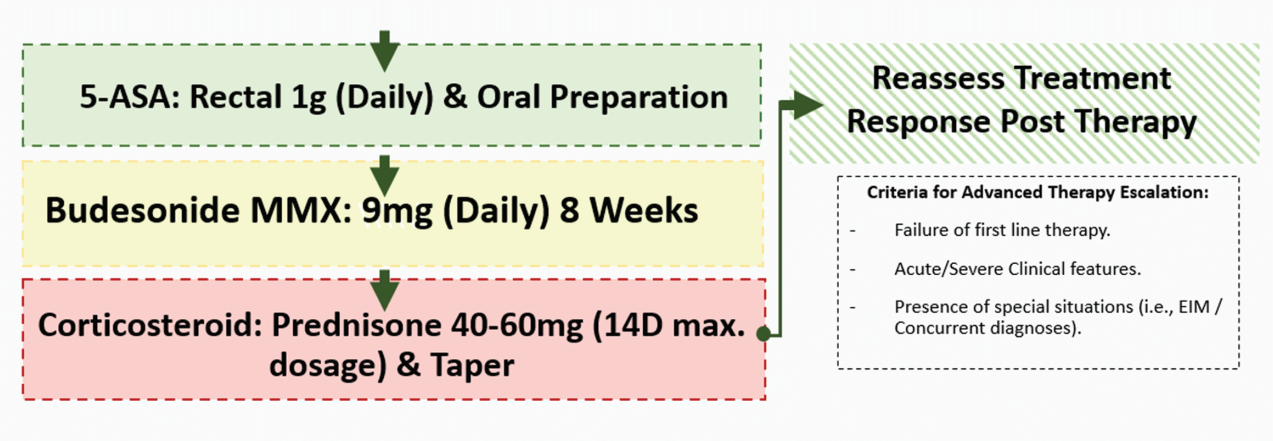

Figure 1. First-line mild to moderate UC (> E1 disease extent) induction therapy algorithm.

Moderate to severe UC

First-line therapy for moderate to severely active UC generally consists of oral systemic corticosteroids to induce remission. A prednisone dosage of 40–60 mg daily, for 7 to 14 days followed by a taper period is typically used.[10] Corticosteroid resistance is defined as a lack of symptomatic response by day 14.[10,14] Following the induction of remission, oral corticosteroid should be tapered and discontinued in favour of thiopurine maintenance therapy or, in selected cases, a trial of oral 5-ASA therapy.[10] Longer term oral corticosteroids lack maintenance efficacy and are associated with a significant side effect profile.[10] In instances where thiopurine therapy is not tolerated, is contraindicated or, increasingly, is not preferred because of its increased risk of infections and certain malignancies, the use of advanced therapies for ongoing maintenance therapy following steroid induction is indicated.

Progression to advanced therapies

When first-line therapy fails to achieve or maintain remission, advanced therapies should be considered. There are multiple considerations prior to the progression of a UC patient to advanced therapy. Safety, both short- and long-term, should remain a foremost priority, while aiming to induce and maintain remission. Additional associated IBD features or comorbidities should be integrated into the advanced therapy-selection process. There are several classes of advanced therapies that have each been shown to provide clinical and endoscopic improvement with induction therapy and reduce the chance of relapse with continued therapy.

Anti-tumour necrosis factor antibodies

Infliximab

The anti-tumour necrosis factor monoclonal antibody, infliximab, was the first biologic drug to be shown to be effective in the treatment of patients who failed or did not tolerate 'conventional therapy' with 5-ASA, steroids, and/or thiopurines.[15,16] Remarkable treatment effect (over placebo) was reported for infliximab from the Active Ulcerative Colitis Trial (ACT) 1 and the ACT2 trials, with induction response of 69%/61% (5 mg/kg/10 mg/kg dosages) at week 8 (vs. 37% with placebo).[15] Maintenance evaluation at weeks 30 and 54 (ACT1 only) noted statistically significant improvements (over placebo) in both clinical and histologic remission.[15]

Two decades after introduction, infliximab continues to be a highly efficacious induction agent, even in comparison to emergent therapies[17] (Table 1). Infliximab combination therapy with azathioprine has been demonstrated to deliver higher rates of corticosteroid-free remission (in comparison to either therapy individually) in anti-TNF naïve UC patients, increasing the potential for therapeutic capture.[18] Combination thiopurine infliximab therapy additionally reduces the incidence of anti-infliximab antibodies, extending the window of potential drug efficacy.[19,20] However, combination therapy may result in marginally increased incidence of infective complications, while use is necessarily limited in young (<20 years of age) male patients given the increased risk of hepatosplenic T-cell lymphoma in this demographic group.[21,22] Other anti-TNF agents, including adalimumab and golimumab, have been shown also to be effective treatments for UC.[23-26] In addition to their beneficial impact on intestinal disease activity, the anti-TNF agents can also be effective against a number of the joint, skin, and eye extraintestinal manifestations (EIMs) and, as such, may be preferred advanced therapies in patients with those particular manifestations.[27,28]

However, anti-TNF agents increase risk of infection and certain malignancies. Some of this risk can be mitigated by screening for latent TB, by immunizations against other pathogens and by cancer prevention and screening strategies such as sun avoidance and cervical cytology testing.

Adalimumab

The UC long-term remission and maintenance with adalimumab (ULTRA)-2 trial was the first to assess both induction and maintenance effect of adalimumab administered with standard dosing.[29] A treatment effect of more than 15% greater clinical response at induction and more than 12% for maintenance therapy was noted.[29] A favourable safety profile was observed with numerically higher rate of adverse events observed in the placebo group.[29] Global trial safety reporting of drug outcomes from multiple indications have confirmed safety, with below expected age-adjusted mortality rates[30] (Table 1).

Subcutaneous administration following induction is a significant step for patient convenience. For patients with

Table 1. Advanced therapies – TNF-α inhibitors.

Anti-TNF-α inhibitors	
Infliximab	Mechanism: Chimeric IgG1 monoclonal antibody with high affinity to tumour necrosis factor-α (TNF-α)
	Originator study outcomes: Active Ulcerative Colitis Trials (ACT-1/ACT-2) – randomized, double-bind, placebo-controlled trials. Clinical response of 61–69 percent with infliximab dosages versus 37% with placebo at week 8, induction assessment. Maintenance assessment at 54 weeks, clinical response of 44–45 percent infliximab dosages versus 20 percent with placebo[15]
	Special considerations: Formation of anti-infliximab antibodies associated with loss of response, variable rates reported across cohorts.[121,122] Low serum infliximab levels in active UC, without antibody formation, may necessitate advanced dosing for treatment effect[123]
Adalimumab	Mechanism: Fully humanized IgG1 monoclonal antibody to TNF-α, with interruption of p55/p75 cell surface reception interactions[29]
	Originator study outcomes: ULTRA-2 – phase 3, multicentre, international, randomized, double-bind, placebo-controlled trial.[29] Clinical response in 50.4% with adalimumab versus 34.6% with placebo at week 8, induction assessment.[29] Clinical response in 30.2% with adalimumab versus 18.3% with placebo at week 52, maintenance assessment.[29] Statistically significant difference over placebo in favour of adalimumab for all primary (i.e., clinical remission, histologic remission) and secondary (i.e. IBDQ response, discontinuation of steroid, sustained endoscopic response) endpoints at induction/ maintenance intervals.[29] Of anti-TNF naïve patients 21.3% achieved clinical remission at week 8[29]
	Special Considerations: Parallel usage in rheumatoid arthritis, ankylosing spondylitis, seronegative arthritides, and psoriasis. Consideration of prioritized usage in UC with concomitant diagnoses. Minimal safety concerns from extensive global trial reporting[30]
Golimumab	Mechanism: Fully humanized IgG1 monoclonal antibody to TNF-α[124]
	Originator study outcomes: PURSUIT Trials – multicentre, randomized, double-blind, placebo-controlled phase 2/3 studies.[33,34,124] Subcutaneous golimumab found to be more efficacious in induction than IV golimumab, and superior to placebo.[124] Clinical response in 51%–54.9% with golimumab vs. 30.3% with placebo at week 6, induction assessment.[24] Clinical response in 47–49.7% with golimumab vs. 31.2%% with placebo at week 54, maintenance assessment.[29] Highest rate of SAE in 100 mg Golimumab maintenance group.[33] Reduced corticosteroid use in 2-year maintenance follow-up[34]
	Special considerations: Parallel usage in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis

concomitant arthritides or dermatopathology, the presence of a therapy for dual indications is also highly beneficial. Being fully humanized adalimumab theoretically carries a lower risk of antibody-mediated loss of response as compared to infliximab.[31] In contrast to infliximab, adalimumab has not been studied or used as an induction agent in acute-severe UC. Ultimately, adalimumab is likely to be surpassed by new therapies with higher absolute treatment effects.[17]

Golimumab

Golimumab has the higher molecular affinity for human TNF-α compared with both adalimumab and infliximab.[32] It was initially thought that this attribute would likely confer increased clinical effect. However, the findings from the phase 3 trial have been generally comparable within class. Clinical induction response was noted to be more than 19% higher compared to placebo.[24] Maintenance assessment at 1 year noted 16% greater treatment response than placebo, with increased steroid-free remission up to 2 years[33,34] (Table 1).

Leukocyte trafficking inhibitor

Vedolizumab

Since its launch, vedolizumab has become widely adopted as an advanced therapy of choice for patients with moderate to severe UC. Its gut-specific mechanism of action provides theoretical safety advantages over other classes of therapy, and it has an excellent short- and long-term safety record (Table 2). Real-world cohorts demonstrate high rates of maintenance of remission, with 60% of patients in clinical remission at 12 months, and anti-TNF naïve patients more likely to achieve remission at all time points.[35]

Support for the first line of vedolizumab is derived from the VARSITY study, a head-to-head comparison of vedolizumab and adalimumab. A higher rate of clinical remission was observed at week 52 with vedolizumab (31.3% Vedolizumab vs. 22.5% adalimumab, CI 2.5 to 15.0; $P = 0.006$); endoscopic improvement was observed more frequently with vedolizumab (39.7% vs. 27.7%, 95% CI 5.2 to 18.5; $P < 0.001$).[36]

The ability to dose escalate (with reduction of administration interval from 8 weekly) further improves the ability to capture partial responders.[37,38] The potential barrier of intravenous administration has also been tackled with development of a subcutaneous formulation for maintenance therapy,[39] with non-inferiority as compared to the intravenous formulation.[40,41]

The application of vedolizumab is best considered as a highly safe, efficacious intervention for patients meeting advanced therapy criteria, generally without the presence of EIMs. Perhaps, most importantly, the gut-specific nature of vedolizumab has meant complete absence of progressive multifocal leukoencephalopathy cases, reported earlier in as many as 1 in 1000 natalizumab-exposed patients.[42,43]

Interleukin-12/23 inhibitors

Ustekinumab

Ustekinumab is a monoclonal antibody to a subunit of the IL-12 and IL-23 molecules. Both interleukins are of a common

Table 2. Advanced therapies – lymphocyte trafficking blockers and anti-interleukin antibodies.

Lymphocyte trafficking blocker	
Anti-integrin antibody – vedoluzimab	-Mechanism: MAB antagonizing α4β7 integrin, on leukocyte subset binding to mucosal address in cell adhesion molecule-1(MAdCAM-1), associated with gut leukocyte trafficking.[125]
	-Originator study outcomes: GEMINI-1 phase 3 study – randomized, double-blind, placebo-controlled trials of vedolizumab in active disease with induction and continued maintenance phase. Week 6 Induction Response and Week 52 maintenance Assessment (endoscopic and clinical). Induction response: 47.1% vs. 25.5% (Vedolizumab vs. Placebo). Maintenance response: 41.8% vs. 44.8% vs. 18.9% (8 weekly vedoluzimab vs. 4 weekly vedoluzimab vs. placebo)[126]
	Special considerations: Vedolizumab does not appear to be linked to increased malignancy incidence or recurrence (in IBD patients with drug exposure in historical-treated malignancy)[112,113]
Sphingosine-1-phosphate receptor (S1PR) Modulator – Ozanimod	-Mechanism: Sphingosine-1-phosphate receptor (S1PR) Modulator. High affinity to S1PR1 and S1PR5[64]
	-Originator study outcomes: True North Study – Phase 3, multicentre, randomized, double-blind, placebo-controlled trial.[66] Induction and maintenance phases using ozanimod hydrochloride 1 mg daily. Randomization of Ozanimod induction responders to maintenance study arms. Statistically higher rates of induction response (47.8% vs. 25.9%, $P < 0.001$) over placebo. Statistically higher rates of clinical response in maintenance period (60% vs. 41.0%; $P < 0.001$) over placebo. Post hoc analysis of initial 10-week ozanimod responders (post-induction) with mucosal healing had higher rates of clinical remission, mucosal healing, and steroid-free remission.[67]
	-Special considerations: S1P receptor modulators are associated with specific adverse events – bradycardia and retinal changes – that require screening of patients at risk. Infection and liver enzyme elevation have been observed[66]
Interleukin 12/23 and interleukin 23 inhibitors	
Ustekinumab	Mechanism: MAB antagonist of the IL-12 and IL-23 p40 subunit[45]
	-Originator study outcomes: UNIFI phase 3, double-blind, placebo-controlled, multicentre trial.[45] Variable dosage induction and assessment at week 8–10% difference in induction group rate clinical remission (130 mg–15.6% and 6 mg/kg 15.5%) to placebo group (5.3%). Statistically significant clinical response at induction of 51.3–61.8% vs. 31.3% (Ustekinumab groups vs. placebo; $P < 0.001$). Subsequent maintenance dosage of 90 mg SC at 8 or 12 weeks, for patients with initial response. Clinical response at maintenance evaluation in 68–71% vs. 44.6% (Ustekinumab groups vs. placebo; $P < 0.001$)[45]
	-Special considerations: Induction response is the best indicator for extended remission. Low or no association with recurrent or novel malignancy[112]
Mirikizumab	Mechanism: IG-G4 MAB antagonist of p19 subunit of IL-23[50]
	Originator study outcomes: LUCENT-1 induction study and LUCENT-2 maintenance study – phase 3 double-blind, multicentre, randomized, placebo-controlled trial.[51,52] Induction protocol of Mirikizumab (300 mg) 4 weekly vs. placebo, with reassessment at week 12.[52] Statistically higher rates of clinical response with Mirikizumab (63.5% vs. 42.2%; $P = 0.00001$).[52] In patients without prior biologic exposure, clinical remission rate was higher than placebo (30.9% vs. 15.8%; $P < 0.001$).[52] The rate of clinical remission at week 52 was statistically significant and higher in favour of Mirikizumab (63.6% vs. 36.9%; $P < 0.001$)[51]
	Special considerations: Greater than 25% maintenance clinical remission even in patients with previous biologic exposure[51]

family, and play role in the potentiation of helper T-cell response in autoimmune inflammatory responses.[44] The UNIFI trial reported 77.6% (498 of 642) of patients exposed to ustekinumab had a clinical response within 16 weeks.[45] In biologic naïve patients, clinical response was observed in 57.9% to 66.7% (vs. 35.8% in placebo arm) at week 8[45] (Table 2).

Serious infections were most common in the placebo group, with no significant incidence of cancer in any group.[45] Overall safety and lack of serious infections in patients treated with ustekinumab remain low.[46] These data suggest that ustekinumab could also reasonably be considered as an option for first-line advanced therapy for biologic naïve patients particularly those with associated psoriasis or psoriatic arthritis[47-49] (Tables 1 and 2) Efficacy in gut, skin, and joint inflammatory disorders suggests that the common pathway remains an important therapeutic target.[44]

Mirikizumab

Mirikizumab is a selective monoclonal antibody against the p19 subunit of IL-23.[50] Initial phase 3 results have shown statistically significant higher rates of clinical responsewith mirikizumab in induction (63.5% vs. 42.2%; $P < 0.001$) and maintenance (63.6% vs. 36.9%; $P < 0.001$).[51,52] Additional safety reporting is awaited, though no drug-related deaths or adverse event rates significantly higher than placebo have been reported to date[51,52] (Tables 1 and 3).

High rates of clinical response and remission in biologic exposed patients are promising. Further quality of life score (IBDQ) reporting and post-hoc analysis have shown significant improvement in comparison to placebo.[53] Over 75% of treated with mirikizumab had improvement in quality of life at week 52.[53]

Janus Kinase (JAK) inhibitors

The Janus Kinase (JAK) inhibitors are small molecule drugs that block a key pathway in the mediation of effect of numerous pro-inflammatory cytokines. There are several JAK inhibitors that have been studied in UC and shown to be effective for both induction and maintenance therapy. A highly efficacious oral agent that can be used for both induction and

Table 3. Colitis assessment/reassessment approach: Elements of evaluation of ulcerative colitis patient necessary to allow appropriate choice of therapy.

- Endoscopy: High-quality endoscopic evaluation, comprehensive visual inspection, segmental biopsies, terminal ileal evaluation
- Histology: Confirmation of typical histological features consistent with UC
- Acute infection: Rule out common pathogens – Campylobacter/E.coli/CMV/parasites/Clostridium Difficile
- Alternative aetiologies: Colonic lymphoma, NSAIDs, checkpoint inhibitor therapy.
- Holistic assessment: Presence of EIM, symptom benchmarking, malignancy or pre-malignancy states

maintenance therapy would be a major breakthrough for UC patients (Table 4).

Tofacitinib

A meta-analysis of 17 studies (including 1,162 UC patients) reporting on real-world tofacitinib response rates, noted 8-week induction remission in 34.7% of patients (95% CI, 29.2%–45.1%), with 6-month remission in 38.3% (95% CI, 29.2–47.5%).[54] Mucosal healing, reported on by six studies, was achieved in 41.9% of patients at week 8 (95% CI, 18.1%–65.6%).[54] These response rates and subsequent real world results are more impressive when considering that tofacitinib was typically used as a second- or third-line advanced therapy following prior biologic failure[54,55] (Table 4).

The possibility of tofacitinib as an efficacious agent has been tempered by its side effect profile. The OCTAVE studies reported rates of infection, skin cancer, dyslipidaemia, cardiovascular, and thrombotic events that were higher than placebo.[55] Meta-analysis findings suggest that incidence of serious adverse events may not be as high as initially suspected.[56,57] However, concerns regarding critical thrombosis and potential for major adverse cardiovascular events (MACE) have limited the broader use of this agent.[57,58] Although not life threatening, the increased incidence of herpes zoster can result in significant morbidity in a significant minority.[59] This risk can be mitigated somewhat by pre-treatment vaccination.

Upadacitinib

The selective JAK inhibitor molecules, such as upadacitinib, appear to have improved efficacy and safety profile compared to non-selective agents. Phase 3 studies of upadacitinib showed high-post induction remission compared to placebo, with adjusted treatment difference of 21.6% in favour of upadacitinib.[60] In maintenance therapy, upadacitinib (combined 15 mg OD and 30 mg OD dose groups) produced an adjusted treatment difference of over 30.7% in comparison to placebo[60] (Table 4).

Safety concerns with respect to thromboembolic events and cardiovascular events arising from non-selective JAK inhibitors seem, thus far, not to be replicated with upadacitinib.[60] The 'UC-1to3' phase 3 induction and maintenance studies report no increase in venous thromboembolic events (VTE) or MACE.[60] Overall, the selective inhibition of JAK-1 may represent a mechanistic difference, with longer term follow-up required to determine true safety profile. Considerable debate continues regarding the actual incidence of VTE that are attributable to JAK inhibition.[57,61,62]

Filgotinib

Filgotinib is an oral JAK-1 preferential inhibitor. Initial reported results from a phase 2/3 study show higher efficacy compared with placebo for both induction and maintenance of remission for the 200 mg daily dosage.[63] Maintenance therapy with filgotinib resulted in 37.2% of patients being in clinical remission at week 58, a 26% absolute gain over placebo.[63]

The clinically efficacious dosage of filgotinib (200 mg) was not reported to be associated with statistically higher rates of infection or serious adverse events (SAE) in comparison to placebo.[63] Indeed, numerically higher rates of SAEs were noted for the placebo group in induction and maintenance phase comparisons (Induction: placebo 5.0% vs. filgotinib 4.7%; maintenance: placebo 7.7% vs. filgotinib 4.5%).[63] No treatment-related deaths were reported. Further real-world outcome reporting and corroboration are required. The reported efficacy as a maintenance therapy represents a potentially significant advance in oral drug treatment – particularly if safety profiles are mirrored in routine clinical use (Table 4).

Sphingosine-1-phosphate receptor (S1PR) modulator

Ozanimod

Ozanimod is a novel pathway agent, acting as a sphingosine-1-phosphate receptor (S1PR) modulator, with high affinity to S1PR1 and S1PR5 receptor subtypes.[64] S1P receptors mediate lymphocyte trafficking from lymph nodes and endothelial integrity.[64,65] Mechanistic studies have shown a reduction in circulating B and T lymphocytes as a result of S1P-receptor modulation.[64]

Phase 3 study results have demonstrated statistically significant higher rates of induction and maintenance of remission in comparison to placebo (induction 18.4% vs. 6.0%, $P < 0.001$; maintenance 47.8% vs. 25.9%, $P < 0.001$).[66] Subjects assigned to maintenance therapy following initial clinical response and demonstrated mucosal healing were found to have higher rates of clinical remission and steroid-free remission at week 52[67] (Tables 1 and 3).

Based on initial results, it is likely that extended therapy will increase the likelihood of maintaining remission. However, real-world incidence rates of AEs including hepatic dysfunction and ocular and cardiac side effects need to be assessed.

Immunomodulators in UC

A number of immunomodulators have demonstrated efficacy in UC and may retain some therapeutic role despite a general trend towards deployment of other advanced therapies.

Ciclosporin is a calcineurin inhibitor and downregulates interleukin synthesis and cell-mediated antigen reactions.[68] Intravenous ciclosporin has significant efficacy (50%–70% reported induction response) in the management of acute severe UC (ASUC), though with a myriad of serious side effects and toxicity issues requiring active drug level monitoring.[69,70] Ciclosporin was employed relatively commonly in steroid refractory UC prior to the introduction of infliximab in the early

Table 4. Advanced therapies – janus kinase (JAK) inhibitors.

Tofacitinib	- Mechanism: Small molecule Janus kinase (JAK) inhibitor. Inhibition of all JAK subtypes, with preferential inhibition of JAK1 and JAK3[55] - Originator study outcomes: OCTAVE 1 and 2 trials – phase 3, international, multicentre, randomized, double-blind, placebo-controlled trials. Following initial induction (tofacitinib 10 mg BD) statistically significant ($P < 0.001$) clinical response was achieved in 55–59.9% at 8 weeks, vs. 28.6–32.8% in placebo.[55] Those demonstrating clinical response were progressed onto the 'OCTAVE SUSTAIN' trial in which 5 mg BD, 10 mg BD and placebo groups were compared. Statistically significant ($P < 0.001$) 52-week clinical response was noted in 51.5% (5 mg BD group), 61.9% (10 mg BD group), and 20.2% (placebo group)[55] - Special considerations: Higher infection rates, skin cancer incidence, dyslipidaemia rates, cardiovascular, and thrombotic events were noted in OCTAVE trial groups exposed to Tofacitinib compared to placebo.[55] High rates of herpes zoster manifestations have been noted from Rheumatoid Arthritis population follow-up data.[127] Efficacy in refractory UC, with consideration needed regarding SE profile[54]
Upadacitinib	- Mechanism: Oral selective JAK-1 inhibitor - Originator study outcomes: U-ACHIEVE (UC-1) and UC-ACCOMPLISH (UC-2) Induction and Maintenance Studies (UC-3) – phase 3, multicentre, international, randomized, double-blind, placebo-controlled studies.[60] Induction with 8 weeks upadacitinib 15 mg, upadacitinib 30 mg o,r placebo (52 weeks).[60] Maintenance study, inclusion of induction responders, with upadacitinib 15 mg, upadacitinib 30 mg, or placebo for 52 weeks.[60] Statistically significant ($P < 0.0001$)higher rates of clinical response achieved with induction upadacitinib 50 mg (UC1 – 60% and UC2 – 63%) vs. placebo groups (UC1 – 26% and UC2 – 27%). Statistically higher rates ($P < 0.0001$) of clinical response achieved in maintenance with upadacitinib (Upadacitinib 15 mg – 63% and Upadacitinib 30 mg – 77%) vs. placebo (19%).[60] - Special considerations: Major cardiovascular events (MACEs) and thromboembolic events adjudicated by external committee – no increased incidence noted in upadacitinib groups.[60] Increased incidence of herpes zoster in upadacitinib maintenance groups vs. placebo.[60] More favourable safety profile, with absence of VTE phenomenon/MACE, reported in comparison non-selective JAK inhibitors.
Filgotinib	- Mechanism: Oral selective JAK-1 inhibitor - Originator study outcomes: SELECTION study – phase 2b/3 double blind, randomized, placebo-controlled, international multicentre trial.[63] Two induction and one continued maintenance study. Induction study with randomization to filgotinib 200 mg, filgotinib 100 mg, or placebo – 11 weeks. Maintenance study, inclusion of induction responders, with continuation of initial filgotinib regimen.[63]Induction dosing with 100 mg filgotinib failed to induce statistically significant remission rates over placebo.[63] Induction dosing with filgotinib 100 mg achieved 35.8–59.2% clinical response vs. filgotinib 200 mg achieving 53.1%–66.5% vs. placebo 17.6–46.7% response. At maintenance interval (58 week) assessment, 100 mg filgotinib achieved 50.6% clinical response vs. 200 mg filgotinib dosage 66.8% vs. continued clinical remission of 32.7–39.3% in the placebo group[63] - Special considerations: Limited induction efficacy at effective dosage (200 mg) overall, with lower efficacy for biologic experienced patients

2000s.[70] Randomized control trial evidence has shown non-inferiority of ciclosporin to infliximab in ASUC.[71] Systematic review and meta-analysis have shown the superiority of both IFX and ciclosporin to placebo, with 1 year colectomy rates with ciclosporin comparable to those with IFX.[72] Ciclosporin may remain a valid option in refractory UC particularly when economic or other factors preclude advanced therapy use.

Tacrolimus is another calcineurin inhibitor, with widespread use following solid organ transplantation.[73] Randomized control trial evidence has shown a clinical response rate of 50%, in contrast to 13.3% with placebo at a 2-week assessment.[74] Systematic review and meta-analysis, including two small RCTs, demonstrated efficacy of tacrolimus in inducing short-term clinical response and producing 70%–90% colectomy-free survival at 12 months.[75] While tacrolimus appears effective in the short to medium term in UC, toxicity and side effect concerns limit general usage.

Thiopurine analogues (i.e., azathioprine and 6-mercaptopurine) have been some of the most widely used drugs in IBD.[76] Long-term reporting from the United Kingdom, on outcomes of approximately 12,000 IBD patients on thiopurine monotherapy, has demonstrated efficacy in the maintenance of remission in UC.[77] The lack of randomized control evidence or trial data for thiopurines in IBD underscores the importance of outcome data in this context.[78] Multi-year thiopurine use has been linked to increased lymphoma risk and increased incidence of non-melanoma skin cancers.[79,80] Ultimately, the role of thiopurines in UC may be to maintain remission in select patients for whom other safer agents are unavailable or are precluded by economic factors.[81–83]

Mycophenolate mofetil is a mycophenolic acid precursor and inhibits T- and B-lymphocyte proliferation via intracellular nucleotide depletio resulting in immune response modulation.[84] While reports of efficacy in induction and maintenance of remission exist, there is a clear paucity of RCT evidence to support broader use.[85,86] Mycophenolate has been directly associated with drug-induced colitis, with this phenomenon creating management ambiguity in the long-term management of remitting-relapsing UC.[87,88]

Methotrexate has demonstrated no superiority to placebo in inducing or maintaining remission in UC in a RCT.[89] Systematic review and meta-analysis of available evidence confirms a lack of efficacy in the treatment of UC with methotrexate.[90]

Choosing advanced therapy

The positioning of the advanced therapies in the UC treatment algorithm is rapidly evolving and becoming more complicated, particularly as more classes of therapy become available – with only limited direct comparative randomized trials.

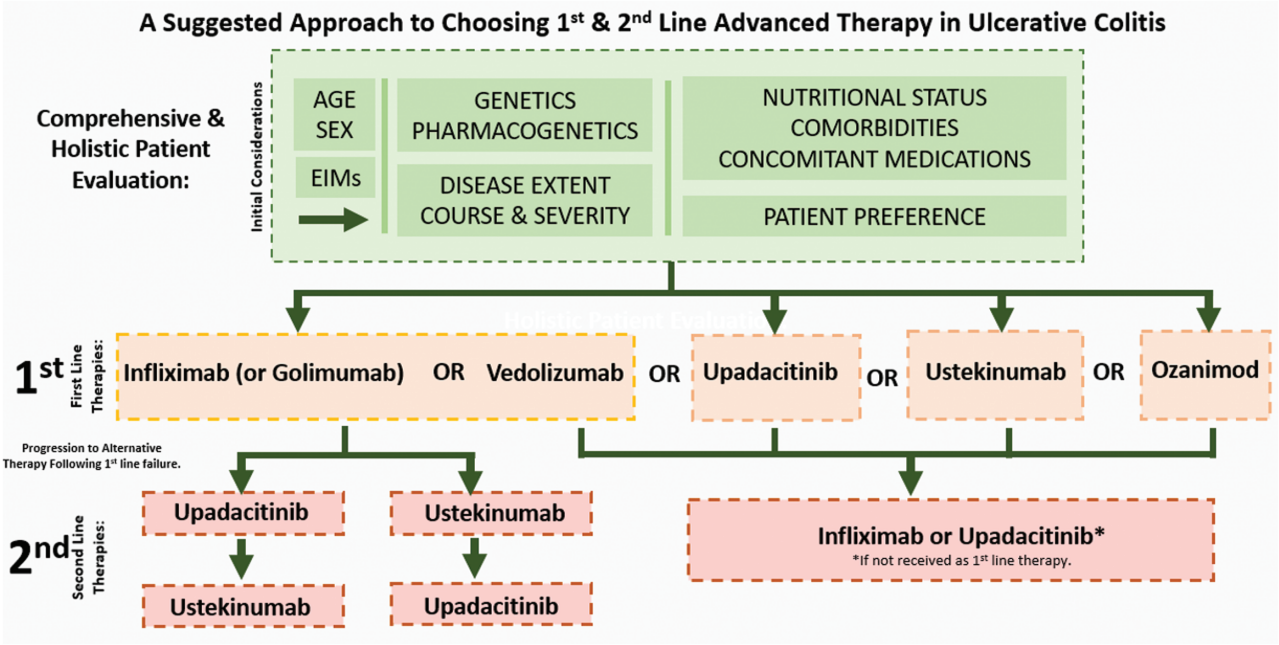

Figure 2. Advanced therapy treatment algorithm.

Both vedolizumab and ustekinumab have demonstrated good efficacy in patients who have not previously been treated with advanced therapy (i.e., bionaive patients), and both have very reassuring safety profiles in clinical trial and real-world outcome reporting. These properties would place these agents as reasonable choices as first-line advanced therapy in UC in the out-patient setting. However, the other agents discussed above have all been shown to be effective for induction and maintenance therapy in bio-naive patients and may be reasonable choices in these patients, particularly when taking into account individual patient factors and preferences (Fig. 2).

Vedolizumab was directly compared to the anti-TNF agent, adalimumab, in the VARSITY trial and found to have superior efficacy when used in standard dosing.[36] However, this should not be taken to mean that vedolizumab is superior to all anti-TNFs. In the absence of direct head-to-head trials involving other therapies, clinicians must turn to other methods of comparison such as network meta-analyses or uncontrolled cohort studies with propensity score matching.

A network meta-analysis comparing infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, and tofacitinib concluded that infliximab was the most efficacious therapy for inducing remission in the bio-naive patient population.[91] This was followed closely by vedolizumab, with vedolizumab being more effective than both infliximab and adalimumab in maintenance of clinical remission and endoscopic improvement.[91] Another subsequent network meta-analysis that also included upadacitinib, filgotinib, and ozanimod concluded that upadacitinib was the most efficacious first-line induction therapy for both induction and maintenance therapy in bio-naive patients.[17]

The placement of vedolizumab as first-line advanced therapy preserves anti-TNFs as an option as second-line therapy. The fact that infliximab has demonstrated efficacy, even in the most severe cases of acute severe colitis, makes it an attractive choice when patients have failed first-line therapy (Tables 1–3). However, it should be recognized that the vast majority of controlled data regarding second-line therapies pertains to the situation in which anti-TNF therapy is used as first-line advanced therapy, and one of the other classes of therapy is used as second- or third-line therapy.

It has been suggested, based upon a recent network meta-analysis that adjusted for differences in maintenance trial design, that upadacitinib is numerically superior to other therapies in induction and maintenance of clinical remission and endoscopic improvement.[17]

When patients have failed one or more advanced medical therapies, it is appropriate to consider the option of surgical management, as it can provide many patients with good long-term quality of life, without need for medical therapy.

Special situations

Although vedolizumab may be considered to be the preferred first-line advanced therapy in UC, there are special situations based on individual patient or disease characteristics or factors that may alter the choice of advanced therapy.

Extraintestinal manifestations

EIMs can occur in roughly 20%–50% of IBD patients with the commonest being arthropathy, uveitis, erythema nodosum, and aphthous ulceration.[92–94] Effective treatment of active intestinal inflammation may or may not directly influence EIM activity, and the various advanced therapies have differing effects on individual EIMs. These differences may influence treatment choice.

The dominant modality of EIM management has been anti-TNF therapy – with demonstrated efficacy in ocular, dermatological, and joint EIMs.[27,28,94] Given that patients with EIM may be at higher risk of aggressive disease, with infliximab as the most potent advanced therapy, providing dual coverage makes therapeutic sense.[28]

Other biologics have demonstrated efficacy in various presentations. Vedolizumab, which is primarily gut-specific,

has been shown to improve enteropathic arthritis, but this is not a generally accepted reason to select vedolizumab over other advanced therapies.[66] JAK inhibitors (i.e., tofacitinib, filgotinib) have been approved for or are under investigation for management of arthridities.[95,96] Meanwhile the anti-interleukin 12/23 agent ustekinumab has been licensed in the management of psoariasis and psoriatic arthritis.[97,98]

Historical practice has given preference to anti-TNF agents which tend to have ameliorating effects on many joint manifestations and may provide benefit for some patients with psoriasis or psoriatic arthritis. However, with the widespread use of alternative advanced therapies, it is likely that further insights into optimal EIM management will emerge.

Pregnancy

All agents are considered safe in pregnancy including during conception and are continued right through pregnancy – with exception of JAK inhibitors and ozanimod which at present are considered contraindicated in pregnancy.[99] The maintenance of remission and minimization of corticosteroid exposure during pregnancy is essential to positive pregnancy outcomes in IBD.[100,101] Conception planning and pregnant patients should be reassured about advanced therapy safety and actively engaged in treatment planning.[101]

UC in an aging population

The bimodal incidence of UC means that new a significant number of new IBD diagnoses will be in patients above the age of 65.[102-104] An estimated 25%–35% of patients with IBD are above the age of 60.[105] This presents unique clinical challenges and management considerations. Elderly patients are more likely to have significant co-morbidities, to be exposed to the risks of polypharmacy and have inherently higher malignancy risk and increased potential for infectious complications.[106-108] Older patients may also have predominantly left-sided disease, with a milder symptom burden or subtle onset.[103,109] Disease course in the elderly may be milder, with decreased advanced therapy need as a proxy indicator.[109] However, in the context of acute severe UC, elderly patients may in fact have higher colectomy rates.[109]

The choice of advanced therapy, if required, therefore, requires careful consideration. The use of JAK inhibitors should be balanced with the potential risk of VTE, cardiovascular events, and herpes zoster reactivation. Use of highly effective Shingrix vaccination to mitigate shingles risk.[110] Upfront use of an anti-TNF may be justified by intended duration of therapy, holistic consideration of patient longevity, and the need to 'preserve' physiological reserves. Elderly patients on infliximab may not have significantly increased risk of adverse events, based on IBD outcome data.[111] Meanwhile, ustekinumab and vedolizumab are not associated with increased malignancy incidence, even with those with prior history of neoplasia.[112,113]

Discussion

The range of available and emerging therapeutic options for UC management is immensely promising for patients. Over the coming years, additional novel agents involving lymphocyte trafficking pathways, selective JAK inhibition, IL-23 inhibition, S1P-receptor modulators and well as PDE4 inhibitors are likely to emerge.[114] The rate of discovery of the past 20 years suggests that further pathways of inflammation mediation will continue to be identified as therapeutic targets, alongside paradigm defining breakthroughs on the role of the intestinal microbiome on intestinal and systemic inflammation.

The possibility of identification of microbiome profiles associated with IBD occurrence, relapse, and remission suggests that microbiome alteration may be a therapeutic target. Faecal microbiota transplant (FMT) has already been examined in cohort studies and RCTs, with demonstrated superiority in induction of remission to placebo in metanalysis.[115-117] Further characterization of high-risk microbiome profiles continues to be a key area of research. Host–microbiome interactions adds an exponential level of complexity to phenotypic expression, which may itself emerge as a therapeutic target for multiple disease processes.[118,119]

The role of dual or multiple concurrent or sequential advanced therapy usage remains undefined. Economic considerations, as well uncertainty over adverse effects currently limit the widespread use of concurrent advanced therapies. However, early data does exist suggesting that 'combination' therapy may be efficacious and have acceptable safety profile.[77] The first dual biologic controlled trial, involving guselkumab and golimumab, shows higher efficacy in combination than with either agent individualy.[120] The core consideration in employing multiple simultaneous or sequential advanced therapies is predominantly whether a cumulative treatment effect significantly surpasses the current modest clinical and endoscopic response rates typically observed with even the most efficacious individual agents.

The increasing prevalence of UC means that more patients will likely require advanced therapy. It is imperative that the healthcare providers caring for these individuals understand the attributes of these therapies in order to optimally leverage their use for patient benefit.

Author contributions

Ronit Das: manuscript concept and design, drafting of the initial version of the manuscript, critical revision of the manuscript for important intellectual content. Hillary Steinhart: manuscript concept and design, critical revision of the manuscript for important intellectual content.

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Data Availability

Not applicable.

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