Positioning biologics and small molecules in the management of moderate to severe ulcerative colitis

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Purpose of review
This review addresses the selection of biologic and small molecule therapy for patients with moderate to severe ulcerative colitis (UC). With several new treatment options approved within the past few years, an update in positioning is timely and relevant.

Recent findings
Updates on the safety and comparative efficacy of approved therapeutic agents for UC are presented. Newly approved therapies including tofacitinib and ustekinumab, as well as where to position these treatments are discussed. Data on the first-ever head-to-head trial of biologic therapy in UC are examined. This review provides an evidence-based overview of the optimal management strategies of patients in both the inpatient and outpatient settings.

Summary
As we move closer towards the goal of personalized therapy for our patients with UC, we hope to better select appropriate and effective treatment options. Newly approved therapies provide us with additional options for management. Future advancements in predictive serologic, mucosal, genetic, and fecal markers can enable us to tailor therapy to an individual patient.

Keywords
biologic, small molecule, ulcerative colitis

INTRODUCTION

We have grown our armamentarium with the approval of new treatments for ulcerative colitis (UC). In order to optimize the positioning of biologics and small molecules in the treatment of moderate to severe UC, we need to evaluate multiple factors that influence selection. We will first break down the options based on mechanism of action, and provide data from clinical trials, real-world settings, and systematic reviews and meta-analyses. We will also provide guidance on selection and positioning of therapy based on severity and outpatient versus hospitalized acute severe UC (ASUC) (See Fig. 1).

Outpatient setting

We should consider several factors when choosing therapy for our outpatients with moderate to severe UC. Patient preference such as oral, intravenous (IV), or subcutaneous (SQ) could impact their adherence as well as cost and coverage. Assessing comorbidities such as cardiac disease, extraintestinal manifestations, or other immune-mediated conditions should impact the decision on which mechanism of action to choose (see Table 1).

Antitumor necrosis factor agents

The antitumor necrosis factor (anti-TNF) agents infliximab (IFX), adalimumab (ADA), and golimumab (GOL) are effective for the induction and maintenance of remission of moderately to severely active UC. All three have demonstrated superiority over placebo in achieving response and remission

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KEY POINTS

- This review addresses the selection of biologic and small molecule therapy for patients with moderate to severe UC.
- Updates on the safety and comparative efficacy of approved therapeutic agents for UC are presented.
- Positioning of therapies based on classification of mechanism of action are discussed.
- This review provides an evidence-based overview of the optimal management strategies of patients in both the inpatient and outpatient settings.

and are recommended as first line options in UC management guidelines [1▪▪,2▪▪].

Combination therapy

When IFX is used as induction therapy, combination therapy with a thiopurine or methotrexate should be considered to increase efficacy and decrease the risk of immunogenicity. Recently, an observational study identified an association between HLA-DQA1∗05 and the development of antibodies against anti-TNF agents [3]. No trials have compared ADA or GOL monotherapy with combination therapy.

Safety

The overall risk of serious infections (requiring hospitalization), in patients treated with TNF antagonist monotherapy or combination therapy with an immunomodulator (IMM) was <1% [2▪▪]. Risks are higher in older patients with comorbidities, whilst combination therapy doubles the risk of opportunistic infections [4], and triples the lymphoma risk compared to monotherapy [5]. However, anti-TNF therapy has been shown lower mortality compared to prolonged corticosteroid therapy [6].

Positioning

In the recent AGA technical review and network meta-analysis of biologic naïve moderate to severe UC patients, IFX demonstrated superiority over ADA (OR, 2.10; 95% CI 1.16–3.79) for clinical and endoscopic remission [2▪▪].

Limited real-world observational studies have suggested a lower risk of hospitalization, corticosteroid use, and serious infections in IFX-treated patients compared to ADA [2▪▪]. IFX was also associated with more rapid resolution of symptoms and greater

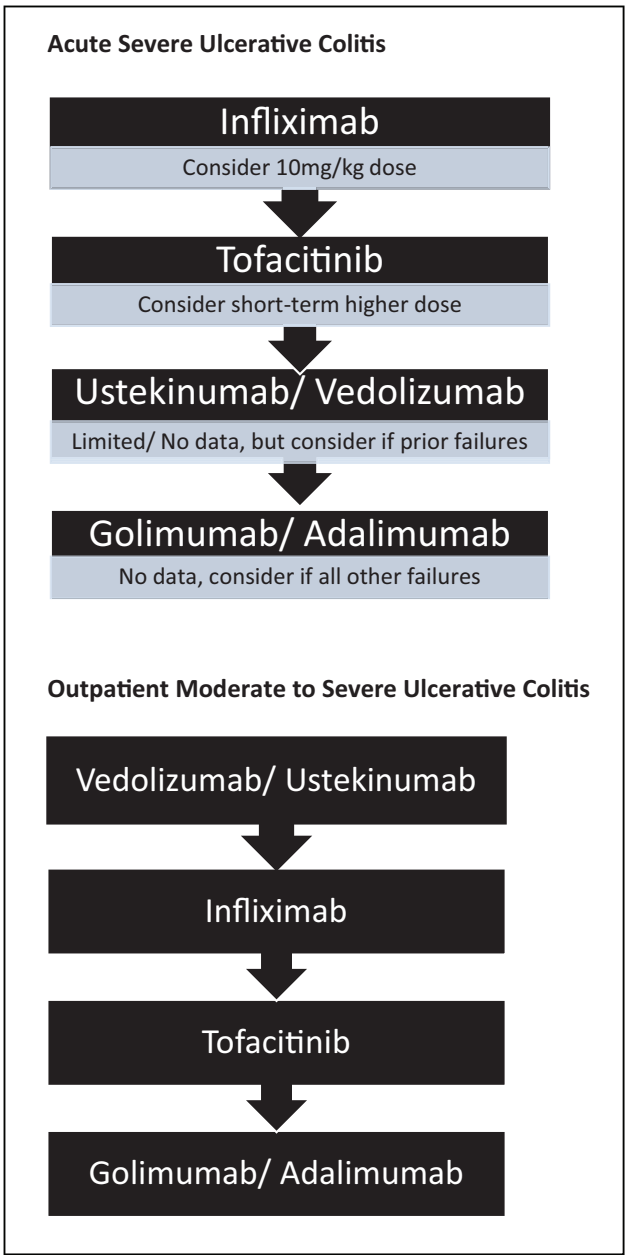

FIGURE 1. Positioning biologic/small molecule therapies.

efficacy for inducing remission than GOL for moderate to severe UC [7]. Furthermore, in the network meta-analysis, the rate of induction of endoscopic remission was higher in IFX compared to GOL [2▪▪].

Although IFX, ADA, and GOL have similar mechanisms of action, differences in pharmacokinetics and bioavailability may impact efficacy. Patient preference in regards to IV versus SQ dosing should also be considered when selecting therapy.

Vedolizumab

Vedolizumab (VDZ) inhibits α4β7-mediated lymphocyte trafficking and since the initial GEMINI

Table 1. Indications and cautions for biologics and small molecule therapy

Medication	Indications	Caution
Infliximab (+biosimilars)	UC, CD, RA, AS, Ps, PsA	CHF, MS, Malignancies (Melanoma, Lymphoma), Infections (TB, Hepatitis B reactivation, opportunistic)
Adalimumab	UC, CD, RA, AS, Ps, PsA, JIA, UV, HS	CHF, MS, Malignancies (Melanoma, Lymphoma), Infections (TB, Hepatitis B reactivation, opportunistic)
Golimumab	UC, RA, PsA, AS	CHF, MS, Malignancies (Melanoma, Lymphoma), Infections (TB, Hepatitis B reactivation, opportunistic)
Vedolizumab	UC, CD	No black box warnings
Ustekinumab	UC, CD, Ps, PsA	No black box warnings Caution: Infections (TB)
Tofacitinib	UC, RA, PsA	Infections (TB, opportunistic), Malignancies (Lymphoma), VTE (?),

AS, Ankylosing Spondylitis; CD, Crohn's disease; CHF, Congestive Heart Failure; HS, hidradenitis suppurativa; JIA, Juvenile Idiopathic Arthritis; MS, Multiple Sclerosis; Ps, Plaque Psoriasis; PsA, Psoriatic Arthritis; TB, Tuberculosis; UC, ulcerative colitis; UV, Uveitis; VTE, Venous Thromboembolism.

trials, additional studies confirm its long-term efficacy and safety in moderate to severe UC treatment. A retrospective review from 14 centers including 303 UC patients showed clinical response of 79% at three months, and clinical remission rates of 60% at 12 months [8]. Confirming our prior knowledge, anti-TNF naive patients had 1.8 times higher rates of clinical remission than anti-TNF exposed ($P < 0.001$).

Long-term follow-up data of VDZ continues to support an excellent safety profile. In approximately 3,000 patients treated for five years no increased risk of opportunistic infection or malignancy was reported [9].

Combination therapy

IMM did not affect efficacy, clearance, or immunogenicity of VDZ in the clinical trials. A multicentered retrospective study of IBD patients (263 with UC), showed no difference in clinical response or remission, endoscopic remission or persistence of therapy with combination therapy vs monotherapy at up to one year [10▪]. This provides additional assurance of VDZ use as monotherapy.

Prognostic factors

Since only about two-thirds of UC patients achieve initial response to therapy, the need for personalized treatment in IBD is of paramount importance. Analyses of GEMINI 1 trial data showed that bio-naïve, 2 years or greater disease duration, moderate baseline endoscopic activity, and higher baseline albumin were independently associated with corticosteroid-free remission during VDZ therapy [11]. This analysis also identified those patients that lacked initial response most benefited from reducing dosing intervals of VDZ.

Positioning

In the first-ever head-to-head trial of biologic therapy in IBD, 769 patients randomized to either VDZ or ADA showed higher rates of clinical remission (31.3% vs. 22.5%; $P = 0.006$) and endoscopic improvement (39.7% vs. 27.7%; $P < 0.001$) with VDZ, but not corticosteroid-free clinical remission (12.6% vs. 21.8%), a secondary outcome measure, respectively [12▪]. Infection rates were lower in the VDZ group, and there were higher rates of improvement in patient-reported outcomes (PROs), quality of life, and histologic remission with VDZ compared to ADA. No dose escalation was allowed in this study limiting some generalizability to clinical practice. Based on mechanism of action, VDZ had traditionally been considered an agent that may take longer for efficacy than anti-TNFs. However, in this study, even at week 14, higher clinical remission was found in the VDZ group (27%) than the ADA group (21%), dispelling this myth [12▪].

A retrospective comparative efficacy study of UC patients who failed a SQ anti-TNF therapy (ADA or GOL) found that more patients treated with VDZ (49%) achieved clinical remission at week 14 compared to IFX (26%, $P = 0.001$) [13]. Furthermore, more patients remained on VDZ therapy at years one and two (80% and 55%) than on IFX (50% and 29%), respectively. This study suggests that VDZ can be successfully used and perhaps preferred in patients who are prior SQ anti-TNF nonresponders.

In the retrospective analysis of VICTORY Consortium data of VDZ use in UC patients with prior anti-TNF exposure (71%), 12-month cumulative analysis showed clinical and endoscopic remission rates of 51% and 41%, respectively [14]. As expected, prior exposure to anti-TNFs was associated with lower rates of clinical and endoscopic remission. Serious AEs and serious infection rates remained low (6% and 4%, respectively) providing real world evidence consistent with clinical trials.

Outcomes from these studies point to a favorable position of VDZ in UC. Markov modeling showed that VDZ use as first line prior to thiopurine or anti-TNF therapy remained the preferred strategy for treatment of moderate to severe steroid dependent UC patients, leading to fewer serious infections and lymphoma diagnoses, and improvement in quality-adjusted life-years, with benefits increasing with longer duration of use [15].

Currently, VDZ is given as an IV infusion. However, the SQ formulation was found to be as effective as maintenance therapy in moderate to severe UC patients who had a clinical response to IV VDZ induction therapy with a favorable safety profile [16▪]. Although not yet available in the United States, this could be a future SQ option for patients.

Ustekinumab

Ustekinumab (UST), an antibody to the p40 subunit of interleukin (IL)-12 and 23, showed efficacy in bio-naïve and bio-experienced patients in randomized control trials (RCTs) [17▪]. As early as week two, UST treated patients had greater reduction in CRP and fecal calprotectin and by week eight, UST was more effective than placebo in clinical response and remission, endoscopic improvement, health-related QOL, and histo-endoscopic mucosal healing. In the maintenance study, UST efficacy was noted again in both bio-naïve and bio-experienced patients with higher rates of steroid-free clinical remission, clinical response and endoscopic and histologic remission in the UST treated group than the placebo. Immunogenicity remained low during both induction and maintenance with only 4.6% developing antibodies [17▪].

Since those achieving histo-endoscopic mucosal healing after induction therapy had lower disease activity at the end of the maintenance study than those with only histologic or endoscopic improvement alone, we should consider early endoscopic and histologic assessment as it may predict long term response [18].

Similar to VDZ, combination of UST with an IMM does not provide additional benefit, with no differences in clinical response or remission, endoscopic remission or persistence of therapy at one year with combination therapy vs monotherapy [10▪].

Safety

UST is safe and well tolerated with serious AE's not commonly reported. No new safety signals have emerged in longer term safety data [19]. In fact, from weeks 44 to 96, AEs, serious AEs, malignancies, and serious infections per hundred patient-years of follow-up were numerically lower in the UST treated groups compared to placebo.

Positioning

With the current efficacy and safety data, UST can be positioned either as first, second, or even third line for moderate to severe UC. Of note, in the UNIFI studies, only a small percentage of patients were VDZ exposed and no patients enrolled had previously failed tofacitinib (TOF) suggesting the need for further studies in those with treatment refractory disease. UST appears to be a durable, safe medical therapy in the UC patient with low rates of immunogenicity and sustainable trough levels with monotherapy. When positioning UST, the clinician should take into account the patient's disease severity, preference for treatment, comorbidities (psoriasis, psoriatic arthritis), and medical coverage.

Tofacitinib

TOF is an oral, Janus Kinase (JAK) inhibitor that preferentially inhibits JAK1 and JAK3 in a dose-dependent manner, is unaffected by age, sex, body weight or disease severity [20], and by blocking several cytokines, provides an opportunity to treat UC through different inflammatory pathways than other biologic therapies. TOF led to clinical remission and mucosal healing during induction and maintenance based on three large RCTs in moderate to severe UC patients [21]. Importantly, there were no differences in TOF efficacy between patients who were previously exposed to anti-TNFs compared to bio-naive patients. TOF has a rapid onset of action with improvement over placebo in PROs of stool frequency and rectal bleeding in as few as three days [22].

Safety

The interim analysis of a rheumatoid arthritis (RA) study suggested that higher than standard doses of TOF for RA at 10 mg twice daily (BID) was associated with increased risk of venous thromboembolic events (VTE). One must note that this study occured in an older patient population with at least one cardiovascular risk factor and higher than recommended dosing. In UC trials, no specific safety signals suggested this risk and the majority of patients were on 10 mg BID dosing.

In 4.4 years of UC clinical trial data for TOF, the most common dose-related AE was herpes zoster infection which had an incidence ratio (IR) of 2.1 in the 5 mg BID group, 6.6 in the 10 mg BID group versus placebo IR of 1.0. [23]. Therefore, it is recommended to immunize all patients starting on TOF with the attenuated shingles vaccine to reduce this risk.

Safety of TOF, evaluated in a real-world cohort of 260 UC patients with UC from centers making up

the TROPIC consortium, showed 16% of patients reported AEs, mostly infections, with five developing herpes zoster infection and two patients on 10 mg BID dosing developing VTE [24]. In another real-world retrospective observational study of 134 UC patients, no VTEs occurred [25]. An analysis of safety outcomes from UC patients on different medical therapies found that PE (IR 0.16 and 0.04) and DVT (IR 0.54 and 1.41) events per 100 patient years were in fact significantly lower in the TOF cohort compared to the anti-TNF cohort, respectively [26].

Positioning

Although studies were also completed in the bio-experienced population, the FDA (due to the ongoing RA study) has required a label change that only allows for TOF use after failure or intolerance to one anti-TNF, limiting use to second-line therapy.

In a prospectively enrolled registry of 123 UC patients on TOF (95% anti-TNF, 62% VDZ, 3% UST experienced), prior VDZ exposure was associated with reduced clinical remission (OR 0.33, 95% CI 0.11–0.94). In a retrospective observational study of 134 UC patients [83% bio-experienced] treated with TOF, 74% responded by week eight and 44% achieved steroid-free remission by week 26, again confirming efficacy as a second-line agent [25]. Predictors of primary nonresponse in their study included younger age ($P = 0.014$) and higher baseline CRP ($P = 0.004$), but not prior biologic exposure. Similar to the original clinical trial data, dose escalation in this real-world cohort also recaptured response in approximately half of patients with secondary loss of response. No significant data exists on TOF use in UC patients that are nonresponders to UST.

A network meta-analysis for moderate to severe UC treatment showed that IFX and VDZ were ranked highest for first-line use, but in anti-TNF experienced, TOF was ranked highest for both induction of clinical remission (OR 11.88) and mucosal healing (OR 4.71) [27]. TOF and VDZ were similar for maintenance of remission. ACG has recently positioned TOF in the UC algorithm either as first-line therapy for moderate-to-severe UC or as second-line therapy in those who have failed an anti-TNF [1▪▪].

Hospitalized acute severe ulcerative colitis

Complications are the highest for the hospitalized ASUC patient as morbidity and mortality increases with emergency colectomy especially with bowel perforation. Our ultimate goal is to use medical therapy to de-escalate disease severity to provide outpatient management.

ANTI-TNF'S

Infliximab

In patients hospitalized with ASUC who do not respond to IV corticosteroids, IFX use should be considered. Patients treated with IFX have decreased rates of colectomy compared to placebo, higher rates of steroid-free remission by 12 months, with persistent benefit at three years follow up [1▪▪]. A recent systematic review and meta-analysis including 2158 ASUC patients found overall colectomy-free survival of 79.7% at three months and 69.8% at 12 months with IFX [28▪]. In patients with severe hypoalbuminemia, high dose induction with 10 mg/kg dosing or accelerated dosing may be considered, although recent studies have not confirmed a benefit [28▪,29,30]. Differences for colectomy-free survival in RCT have not been seen in the use of IFX compared to cyclosporine for ASUC [31]. Therefore, the decision to use IFX or cyclosporine for ASUC should be based on provider experience and drug availability.

Adalimumab and golimumab

There are currently no data to support the efficacy of ADA or GOL use in ASUC [1▪▪,2▪▪].

Vedolizumab

There is currently no role for the use of antiintegrins in hospitalized ASUC. Although no RCTs evaluated VDZ use in ASUC, one retrospective study of 39 steroid refractory UC patients (31 of whom were hospitalized with ASUC) who were given a calcineurin inhibitor along with VDZ, prevented colectomy in two thirds of the patients [32]. Despite limited data, VDZ should not necessarily be excluded and can be considered in the hospitalized ASUC patient that are nonresponders to anti-TNF therapy, or where other biologic or small molecule therapies are contraindicated.

Ustekinumab

There are currently limited data to support the efficacy of UST use in ASUC.

Tofacitinib

Limited but emerging data suggests a role for TOF in ASUC. In a case series of four patients hospitalized with ASUC, off-label use of TOF 10 mg TID provided rapid improvement in clinical symptoms within 3 days preventing urgent colectomy in all patients [33]. Another series of four steroid refractory ASUC patients found that addition of TOF (3 given 10 mg BID and 1 escalated to 15 mg BID) led to

improvement, avoidance of emergent colectomy, and no hospital readmission at 90 days or serious AEs [34]. Another retrospective case series showed five of seven anti-TNF and steroid-refractory patients receiving TOF 10 mg BID had rapid clinical response with CRP normalization and early hospital discharge after TOF initiation [35]. However, two patients (one with CMV colitis) required colectomy during admission while two others required surgery following readmission within 90 days.

These studies suggest that standard or off-label short term high dose (30 mg/day) TOF may benefit hospitalized ASUC patients in avoiding emergent colectomy. Risk of AEs should be discussed with the patient, and dose de-escalation should be planned for maintenance.

CONCLUSION

We currently have several options in managing moderate to severe UC. Personalization of therapy has not yet come to full fruition but with future biomarker studies, we hope to obtain more accuracy in who will respond to therapy. In the meantime, we should keep in mind severity of disease, but also patient preference of route of administration, ease of accessibility based on insurance and coverage, and patient's comorbidities in choosing appropriate therapy.

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Conflicts of interest

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K.G. has no conflicts of interest to report.

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