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INFLAMMATORY BOWEL DISEASE (S HANAUER, SECTION EDITOR)

Maneuvering Clinical Pathways for Ulcerative Colitis

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Abstract

Purpose of Review Recent years have brought about several advances in the treatment of patients with ulcerative colitis (UC). Here, we discuss salient recommendations of recent treatment guidelines; review the efficacy, safety, and real-world data of vedolizumab and tofacitinib; appraise their place vis-à-vis established agents; and consider the newly proposed approaches of risk-stratified and treat-to-target therapy.

Recent Findings Once daily oral mesalamine dosing is equivalent to split dosing in mild–moderate UC. Real-world data are accumulating on the effectiveness and safety of vedolizumab for moderate to severe UC, while there are few such data on the most recently approved agent, tofacitinib. High-dose infliximab is being investigated for severe UC. New approaches are challenging the established paradigm of selecting therapy based on current disease activity. The risk-stratified approach incorporates long-term risk as well as the current burden of inflammation. The treat-to-target approach aims at improved long-term outcomes by adjusting therapy to resolve intestinal inflammation.

Summary The therapeutic options for UC are continually expanding. Risk-stratified therapy and the treat-to-target approach represent paradigm shifts in UC management. Optimal disease control requires an individualized approach that takes into consideration current inflammatory burden, long-term risk, patient preferences, and ongoing assessment of response to treatment.

Keywords Ulcerative colitis · Inflammatory bowel disease · Vedolizumab · Tofacitinib

Introduction

Until the late 1990s, the treatment arsenal of ulcerative colitis (UC) was restricted to mesalamine (5-ASA), corticosteroids, and thiopurines. The introduction of anti-tumor necrosis factor α (anti-TNF-α) agents represented a milestone in UC management [1]. Moreover, over the next few years, investigators recognized the importance of mucosal healing in improving long-term outcomes [2]. Although anti-TNF-α agents improve disease control, enhance quality of life, and prevent complications, primary non-response and loss of response (the latter, in large part, due to high rates of immunogenicity) remain significant challenges. Against this backdrop, the newly approved agents (vedolizumab and tofacitinib) hold the promise of producing significant therapeutic gains. The purpose of this article is to discuss salient recommendations of recently updated treatment guidelines; review the efficacy, safety, and real-world data on vedolizumab and tofacitinib; appraise their place vis-à-vis established agents; and discuss the newly proposed approaches of risk-stratified and treat-to-target therapy.

This article is part of the Topical Collection on *Inflammatory Bowel Disease*

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Treatment Guidelines

Mild UC

The European Crohn's and Colitis Organization (ECCO) in 2017 [3] and the American College of Gastroenterology (ACG) [4••] in 2019 updated their guidelines for the management of mild, moderate, and severe UC. The American Gastroenterological Association (AGA) guidelines in 2019 addressed only induction of mild UC [5••]. Although UC severity has traditionally served as the basis for selecting therapy, there are no uniformly accepted definitions of disease severity. In the AGA technical review, mild-to-moderate UC

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was defined as "<4–6 bowel movements (BM's) per day, mild–moderate rectal bleeding, absence of constitutional symptoms, and low inflammatory burden, based on biochemical and endoscopic assessment, and absence of features suggestive of high disease severity (e.g., absence of deep endoscopic ulcers, high inflammatory burden, repeated hospitalizations, and steroid-dependence)" [5••]. The ACG defined mild UC as < 4 BMs per day; intermittent rectal bleeding; mild, occasional urgency; normal hemoglobin; erythrocyte sedimentation rate (ESR) < 30 mm/h; elevated C-reactive protein (CRP); fecal calprotectin > 150–200 μg/g; Mayo endoscopic subscore of 1; and UC endoscopic index of severity (UCEIS) of 2–4 [4••]. Finally, ECCO defined mild UC as < 4 bloody BMs (per the Truelove and Witts classification) or ≤ 4 BMs daily, with or without blood (per the Montréal classification), with normal pulse, temperature, hemoglobin, ESR, and CRP [3].

For patients with extensive UC, all guidelines endorsed oral 5-ASA. Moreover, the guidelines suggested combined oral and rectal 5-ASA over oral 5-ASA alone. Whereas the AGA guidelines recommended standard 5-ASA dosing (2–3 g/day) or diazo-bonded 5-aminosalicylates (olsalazine and balsalazide) over sulfasalazine (strong recommendation, moderate-quality evidence) [5••], ACG and ECCO did not make any recommendations regarding the relative positioning of 5-ASA, diazo-bonded 5-aminosalicylates and sulfasalazine. The AGA technical review stated that oral 5-ASA doses of 2 g/day to 3 g/day (standard) or > 3 g/day (high) were more effective than doses of < 2 g/day (low) for the induction and maintenance of remission (moderate quality of evidence) [6]. The AGA guidelines [5••] recommended starting at the standard 5-ASA dose of 2–3 g/day (strong recommendation, moderate-quality evidence). In patients with a suboptimal response to standard dose 5-ASA, the AGA suggested high-dose 5-ASA (> 3 g/day) along with rectal 5-ASA (conditional recommendation, moderate-quality evidence for induction of remission; conditional recommendation, low-quality evidence for maintenance of remission). The ACG guidelines were slightly different in that they *suggested* low-dose 5-ASA (2–2.4 g/day) over high-dose 5-ASA (4.8 g/day) (conditional recommendation, very low quality of evidence). For patients with proctitis or left-sided disease, rectal 5-ASA is the treatment of choice and is preferred over rectal steroids. In these patients, oral 5-ASA can be used either as adjunctive therapy for patients with an incomplete response to rectal 5-ASA or as an alternative for patients who prefer the convenience of oral medications.

With regard to the frequency of oral 5-ASA dosing, the AGA suggested once-daily dosing rather than more frequent dosing (conditional recommendation, moderate quality of evidence) [5••]. The ACG recommended either once daily or more frequently dosing "based on patient preference to optimize adherence, as efficacy and safety are no different" (strong recommendation, moderate-quality evidence) [7]. The equivalence of these dosing strategies was reaffirmed in a recent, 48-week-long, non-inferiority trial [8] that randomized 602 subjects with UC in clinical remission to 2.4 g/day of pH-dependent–release mesalamine (Asacol®) given once daily or divided in three daily doses of 0.8 g. The non-inferiority margin was 10%. Non-recurrence rates were 88.4% and 89.6%, respectively, with a 95% confidence interval of − 6.2 to 3.7, i.e., within the non-inferiority margin. Compliance rates (97.7% and 98.1%, respectively) were comparable. Since frequent mesalamine dosing is associated with lower compliance rates in the real-world setting [9, 10], once daily dosing is the preferred strategy.

Besides 5-ASA, another option for mild–moderate UC is budesonide MMX. Budesonide has minimal systemic absorption due to extensive first-pass hepatic metabolism, while the MMX technology allows for drug release throughout the colon. In the registry trials (CORE-1 and CORE-2), budesonide MMX 9 mg daily (but not 6 mg daily) produced significantly higher rates of clinical remission and endoscopic improvement at 8 weeks compared with placebo [11, 12]. A more recent trial demonstrated the efficacy of budesonide MMX in patients with mild-to-moderate UC refractory to oral 5-ASA [13]. In this study, 510 patients with active disease while on 5-ASA ≥ 2.4 g/day were randomized to budesonide MMX 9 mg daily or placebo for 8 weeks. Baseline mesalamine was continued. In the modified intention-to-treat population, the rates of combined clinical and endoscopic remission at week 8 were 13.0% and 7.5% in the budesonide MMX and placebo arms, respectively ($P = 0.049$). The AGA guidelines suggested standard-dose oral 5-ASA (or diazo-bonded 5-ASA) over budesonide MMX for the induction of remission of mild–moderate UC (conditional recommendation; low-quality evidence) [5••]. Finally, the AGA *suggested* and the ACG *recommended* adding budesonide MMX or prednisone in patients with mild–moderate UC refractory to optimized oral and rectal 5-ASA.

With regard to maintenance therapy, the ACG recommended rectal 5-ASA for patients with proctitis and oral 5-ASA (≥ 2 g/day) for patients with left-sided or extensive UC [7]. Patients who require higher doses of oral 5-ASA to induce remission are typically treated with higher maintenance doses, but there is no robust evidence supporting this practice. In general, the ECCO recommendations for the induction and maintenance of mild–moderate UC were similar to those of the AGA and ACG. ECCO stated that rectal 5-ASA is an alternative to oral 5-ASA in left-sided UC (evidence level (EL) 1), and that combination oral and rectal 5-ASA may be used as second-line maintenance treatment (EL1) [14]. Notably, two RCTs found that combination of oral 5-ASA plus intermittent 5-ASA enemas was more effective than oral 5-ASA alone in maintaining remission [15, 16].

Moderate UC

The ACG guidelines, published in 2019 and incorporating tofacitinib, constitute the most up-to-date guidance for the treatment of moderate to severe UC [4••]. The ACG defined moderate to severe UC as > 6 BMs daily, frequent rectal bleeding and urgency, hemoglobin < 75% of normal, ESR > 30 mm/h, elevated CRP, fecal calprotectin > 150–200, Mayo endoscopic subscore of 2–3, and UCEIS of 5–8 [4••]. The ACG recommended systemic corticosteroids, anti-TNF-α agents (i.e., infliximab, adalimumab, golimumab), vedolizumab, or tofacitinib for the induction of remission [4••]. When infliximab is used as induction therapy for moderately to severely active UC, the ACG recommended combination therapy with a thiopurine (strong recommendation, moderate quality of evidence) [4••]. The thiopurines may be used as maintenance therapy in patients who achieve remission with corticosteroids (conditional recommendation, low quality of evidence), but these should not be used as monotherapy to achieve induction. The ACG recommended vedolizumab or tofacitinib after failure of anti-TNF-α therapy. Like the ACG, the ECCO recommended anti-TNF-α therapy, preferably combined with thiopurines, at least for infliximab, as one of several options for the treatment of steroid-dependent and steroid-refractory UC [3]. The ECCO guidelines differ from those of the ACG in that tacrolimus was offered as an option in patients with steroid-refractory UC [3].

Recent studies have examined the place of 5-ASA agents after escalation to biologic therapy. Ungaro et al. [17•] examined 3589 patients across two national databases (the USA and Denmark) and found that discontinuation of 5-ASA within 90 days of starting biologic therapy was not associated with adverse clinical outcomes, such as new steroid use, UC-related hospitalization, or surgery. Similar results were found in a pooled analysis of 2183 patients from the registry trials of infliximab and golimumab [18] and in 100 patients treated with vedolizumab [19]. The ACG suggested against using 5-ASA in patients with moderately to severely active UC who have failed 5-ASA therapy and are being induced with an anti-TNF-α agent (conditional recommendation, low quality of evidence) [4••].

Severe UC

The most recent guidelines for acute severe UC (ASUC) are those of ECCO (2017) [3] and ACG (2019) [4••]. Primary therapy consists of intravenous (IV) corticosteroids. When IV steroids fail, options include infliximab, IV cyclosporine, tacrolimus (in the ECCO guidelines), and proctocolectomy. Both guidelines emphasize the importance of excluding infection; endoscopic assessment of disease severity; treatment of anemia; correction of fluid and electrolyte disturbances; prophylaxis against thromboembolism; avoidance of NSAIDs, opioids, and anticholinergic agents; use of antibiotics and total parenteral nutrition only when indicated; and combined management by the gastroenterologist and the colorectal surgeon.

The increased inflammatory burden of ASUC may necessitate higher infliximab doses [20]. A recent meta-analysis found that the outcomes of dose-intensified induction were not significantly different compared to standard induction. However, these results were confounded by the greater inflammatory burden in patients who received intensified therapy [21]. In a retrospective series, 132 patients received standard infliximab therapy, while 81 received accelerated infliximab therapy (> 5 mg/kg at shorter intervals). There were no baseline differences between the groups, including levels of C-reactive protein or albumin. Rates of in-hospital colectomy were 8% and 9%, respectively (adjusted odds ratio, 1.35; 95% CI, 0.38–4.82). Similarly, there were no significant differences in the colectomy rates at 3 months, 6 months, 12 months, or 24 months. In the accelerated group, an initial dose of 10 mg/kg was associated with lower colectomy rates compared to an initial dose of 5 mg/kg followed by subsequent doses of ≥ 5 mg/kg [22]. Randomized trials are needed to assess high-dose infliximab in ASUC. The salient recommendations of recent guidelines are listed in Table 1.

Vedolizumab

Pharmacodynamics and Pharmacokinetics

Vedolizumab, approved for the treatment of UC in the USA in 2014, is a fully humanized, monoclonal IgG1 anti-α4β7 antibody. Vedolizumab blocks the binding of the α4β7 integrin expressed on circulating blood T cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed on gut endothelial cells. In addition to gut-selective blockade of lymphocyte trafficking, other mechanisms of action may be at play [23]. This hypothesis is further supported by the observation that full α4β7 occupancy is evident at very low drug concentrations and is unrelated to response status [24]. The half-life of vedolizumab is 25.5 days [25]. Predictors of increased drug clearance include the presence of anti-drug antibodies, low albumin concentration (< 3.2 g/dl), high body weight (≥ 120 kg), and higher endoscopic score [25]. In contrast, concomitant immunomodulators, C-reactive protein, and fecal calprotectin levels do not predict drug clearance [25]. In the combined populations of the pivotal GEMINI 1 and GEMINI 2 trials ($n = 1434$), 4% of patients had anti-drug antibodies at any time during up to 52 weeks of treatment [24]. Although only 0.6% had persistent anti-drug antibodies, the rate of immunogenicity rose to 10% after patients stopped the drug. Compared to vedolizumab monotherapy, concomitant immunomodulators decreased the formation of anti-drug antibodies in patients who received interrupted vedolizumab

Table 1 Salient recommendations of the recent guidelines for the treatment of UC

Mild disease	1. Rectal 5-ASA is the first-line inductive therapy for proctitis or left-sided UC Comments: (a) Rectal 5-ASA is preferred over rectal steroids, and (b) oral 5-ASA can be used either as an adjunctive therapy for patients with incomplete response to rectal 5-ASA or as an alternative for patients who prefer the convenience of oral medications 2. Combination oral (2–3 g/day) and rectal 5-ASA is suggested over oral 5-ASA alone for the induction of remission in patients with extensive or left-sided UC 3. Once daily 5-ASA dosing is suggested over more frequent dosing 4. Standard dose 5-ASA (2–3 g/day) is recommended over budesonide MMX for induction in patients with extensive UC 5. Adding prednisone or budesonide MMX is recommended in patients who have mild UC (regardless of disease extent) and are failing optimized oral and rectal 5-ASA 6. Oral 5-ASA (≥ 2 g/day) is recommended for maintenance in patients with left-sided or extensive UC Comments: (a) Rectal 5-ASA is an alternative to oral 5-ASA in left-sided UC, (b) combined oral and rectal 5-ASA may be used for maintenance, and (c) patients who require higher doses of oral 5-ASA to induce remission are typically treated with higher maintenance doses, but there is no robust evidence supporting this practice. 7. Rectal 5-ASA is recommended for maintenance in patients with proctitis
Moderate disease	1. Systemic corticosteroids, anti-TNF-α agents (infliximab, adalimumab, golimumab), vedolizumab, and tofacitinib are recommended for the induction of remission 2. There are no recommendations regarding the relative positioning of these agents in inducing remission 3. When infliximab is used as an induction therapy for moderately to severely active UC, combination therapy with a thiopurine is recommended over infliximab monotherapy 4. After failure of anti-TNF-α therapy, options include vedolizumab or tofacitinib 5. The ACG suggested against using 5-ASA in patients with moderately to severely active UC who have failed 5-ASA therapy and are being induced with an anti-TNF-α agent
Severe disease	1. Primary therapy consists of intravenous corticosteroids 2. When intravenous steroids fail, options include infliximab, IV cyclosporine, tacrolimus (in the ECCO guidelines), and proctocolectomy

from 18 to 3% [24]. Among patients on continuous vedolizumab, anti-drug antibodies were observed in 4% of those on vedolizumab alone versus 3% among those on combination therapy [24]. In summary, vedolizumab immunogenicity rates are lower than those of the anti-TNF-α agents. Similar to the anti-TNF-α agents, interrupted vedolizumab therapy induces anti-drug antibodies. While concomitant immunomodulators reduce the immunogenicity of interrupted therapy, immunomodulators do not have any effect on the already low immunogenicity of scheduled therapy.

Efficacy

In the pivotal induction trial (GEMINI 1) [26], patients were randomized to intravenous vedolizumab (300 mg) or placebo at weeks 0 and 2 and were evaluated at week 6. Response rates at week 6 were 47.1% and 25.5% in the vedolizumab and placebo arms, respectively (difference with adjustment for stratification factors, 21.7%; 95% CI, 11.6–31.7%; $P < 0.001$). Similarly, vedolizumab was superior to placebo in the induction of remission (16.9% vs. 5.4%; $P = 0.001$) and mucosal healing (40.9% vs. 24.8%; $P = 0.001$) (PMID: 23964932). In the maintenance trial, vedolizumab responders from the induction trial or a separate open-label study were randomized vedolizumab every 8 weeks, vedolizumab every 4 weeks, or placebo for 52 weeks. At week 52, clinical remission rates were 41.8%, 44.8%, and 15.9%, respectively (adjusted difference, 26.1% for vedolizumab every 8 weeks vs. placebo [95% CI, 14.9–37.2; $P < 0.001$] and 29.1% for vedolizumab every 4 weeks vs. placebo [95% CI, 17.9 to 40.4; $P < 0.001$]). The frequency of adverse events was similar in the vedolizumab and placebo arms.

Safety

Colombel et al. [27•] analyzed the combined safety data ($n = 2932$; > 4000 patient-years of exposure) from two phase II and four phase III trials in IBD patients. The infection rate for vedolizumab was 63.5/100 patient-years (PY) compared with 82.9/100 PY for placebo. The rates of serious infection were 4.3/100 PY versus 3.8/100 PY for vedolizumab and placebo, respectively. Independent risk factors for serious infection in UC included prior failure of anti-TNF-α (HR, 1.99; 95% CIs, 1.16–3.42) and narcotic analgesic use (2.68; 1.57–4.58). Infusion-related reactions were reported in ≤ 5% of patients in each trial.

In the VICTORY consortium ($n = 1087$, CD = 650 and UC = 437) [28], serious infections occurred in 6.3% of patients (7.9/100 PY). Independent predictors of serious infection were active smoking (odds ratio (OR), 3.39) and the number of concomitant immunosuppressants (steroids or immunomodulators; OR, 1.72 per agent) [28]. Like other IgG1 monoclonal antibodies, vedolizumab crosses the placenta. Most, but not all, safety reports are reassuring in the setting of pregnancy [29–31]. The AGA IBD Parenthood Project Working Group recommended maintaining pre-pregnancy dosing, continuing dosing throughout all 3 trimesters, and resuming postpartum [32]. If possible, the working group

suggested planning the final pregnancy dose 6–10 weeks before the estimated date of confinement (or 4–5 weeks before the estimated date of confinement with every 4-week dosing).

Real-World Experience

Several studies from around the world have reported real-world experience with vedolizumab. In the VICTORY consortium ($n = 321$), 12-month cumulative rates of clinical and endoscopic remission were 51% and 41%, respectively [33•]. In the ENEIDA registry ($n = 244$), the rate of vedolizumab discontinuation was 27.6% per PY of follow-up [34]. A meta-analysis of real-world studies ($n = 9486$; $n = 4532$ CD; $n = 3216$ UC; $n = 1738$ IBD unspecified/indeterminate/other) found that vedolizumab was more effective in UC than CD [35]. Corticosteroid-free remission rates at 12 months were 42% and 31% for UC and CD, respectively. Another meta-analysis found that the pooled incidence rate of loss of response in UC was 39.8 per PY. Dose intensification restored response in 53.8% of secondary non-responders [36].

Predictors of Response

An important unmet need with inductive therapies concerns the prediction of late response and non-response. In multivariate analysis of the pivotal GEMINI 1 trial [26], predictors of response included higher drug levels and anti-TNF-α–naïve status [35, 37]. Multivariate analysis of the VICTORY consortium showed that prior anti-TNF-α exposure was associated with a lower probability of clinical (HR, 0.53; 95% CI, 0.38–0.75) and endoscopic remission (HR, 0.51; 95% CI, 0.29–0.88) [33•]. The overall colectomy rate at 12 months was 13%, 2% in the anti-TNF-α–naïve patients compared to 19% in the anti-TNF-α–experienced patients [33•].

Although vedolizumab improved rectal bleeding and diarrhea by 3 weeks of therapy in GEMINI 1, further gains were observed at weeks 4 and 6. However, these improvements were restricted to anti-TNF-α–naïve patients [38]. Dulai et al. [39] developed and validated a scoring tool for predicting treatment outcomes with vedolizumab in UC. Factors independently associated with steroid-free remission were the absence of previous anti-TNF-α exposure (+ 3 points), disease duration ≥ 2 years (+ 3 points), baseline endoscopic activity (moderate vs. severe) (+ 2 points), and baseline albumin concentration (+ 0.65 points per g/l). Patients were stratified into low (≤ 26 points), intermediate (> 26 to ≤ 32 points), or high (> 32 points) probability of response groups. The higher probability group more rapidly achieved symptom activity reductions and attained higher rates of steroid-free remission ($P < 0.001$). In the validation set, a 26-point cutoff value showed high sensitivity (93%) for identifying non-responders.

Data on the utility of therapeutic drug monitoring for vedolizumab are still being generated. To determine optimal trough concentrations associated with clinical remission, a propensity score–based case-matching analysis was performed using data from the GEMINI 1 trial [40]. The investigators adjusted for potential confounder that can affect vedolizumab clearance, including age, weight, anti-TNF-α exposure history, serum albumin, and fecal calprotectin levels. Optimal trough levels were 37.1 μg/ml, 18.4 μg/ml, and 12.7 μg/ml at 6 weeks, 14 weeks, and steady state, respectively.

Use in Specific Clinical Settings

Due to its slower onset of action compared with anti-TNF-α agents and steroids, vedolizumab cannot be recommended in patients with severe disease. Preliminary studies suggest that vedolizumab is less effective than anti-TNF-α agents in the treatment of extraintestinal manifestations of IBD [41] and no more effective than placebo in controlling UC-associated arthritis/arthralgias [42]. Perioperative vedolizumab use is not associated with increased infectious complications in UC patients who undergo colectomy [43–45]. In a recent multicenter study that compared the safety and efficacy of anti-TNF-α ($n = 131$) and vedolizumab ($n = 103$) in IBD patients who were 60 years or older (range 60–88 years), therapies were similarly safe and effective at 6 months and 12 months [46].

Tofacitinib

Pharmacodynamics and Pharmacokinetics

Tofacitinib inhibits the Janus kinase (JAK) intracellular enzymes [47]. Binding of cytokines and growth factors to their cognate receptors on the cell membrane leads to JAK phosphorylation and dimerization (JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). In turn, activated JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) proteins, which modulate genes regulating cellular hematopoiesis and immune cell function. In vitro, tofacitinib inhibits the activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 with IC_{50} of 406 nM, 56 nM, and 1377 nM, respectively [48]. However, the contribution of the inhibition of each JAK dimer to the effectiveness of tofacitinib is unknown.

Tofacitinib bioavailability is 74%. Peak plasma concentration is reached within 0.5–1 h. The elimination half-life is ~ 3 h, and steady-state concentrations are achieved in 24–48 h [48]. There is no clinically meaningful effect of age, sex, body weight, or disease severity at baseline (i.e., baseline albumin

level and Mayo score) on oral clearance and thus on average plasma concentration [49••].

As the drug is cleared via the liver (70%) and kidneys (30%), it should be dosed at 5 mg twice daily (rather than at the standard dose of 10 mg twice daily) in patients with moderate hepatic impairment or moderate or severe renal insufficiency, and it should be avoided altogether in patients with severe hepatic impairment. Tofacitinib is metabolized primarily via cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, via CYP2C19. The dose should be lowered to 5 mg daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole) or medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Conversely, exposure is decreased when the drug is coadministered with potent CYP3A4 inducers (e.g., rifampin) [48].

Efficacy

The efficacy of tofacitinib was established in the pivotal induction (OCTAVE 1 and OCTAVE 2) and maintenance (OCTAVE Sustain) trials [49••]. In OCTAVE 1 ($n = 598$) and OCTAVE 2 ($n = 541$), patients with moderately to severely active UC despite previous conventional or anti-TNF-α therapy were randomized to tofacitinib (10 mg twice daily) or placebo for 8 weeks. Remission rates in the tofacitinib and placebo arms at week 8 were 18.5% versus 8.2% ($P = 0.007$), respectively, in OCTAVE 1, and 16.6% versus 3.6% ($P < 0.001$), respectively, in OCTAVE 2. Reductions in diarrhea and rectal bleeding were seen as early as 3 days of treatment [50]. In the OCTAVE Sustain trial, 593 responders to induction therapy were randomized tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. Remission at 52 weeks occurred in 34.3% of the patients in the 5 mg tofacitinib group and 40.6% in the 10 mg tofacitinib group versus 11.1% in the placebo group ($P < 0.001$ for both comparisons with placebo) [49••]. Similar to clinical remission, tofacitinib treatment was associated with significantly higher rates of mucosal healing at week 8 (31.3% vs. 15.6% [$P < 0.001$] in OCTAVE 1 and 28.4% vs. 11.6% [$P < 0.001$] in OCTAVE 2) and week 52 (45.7% for tofacitinib 10 mg b.i.d., 37.4% for tofacitinib 5 mg b.i.d., and 13.1% for placebo [$P < 0.001$] for both tofacitinib and placebo comparisons) [49••].

Safety

In an analysis of the phase 2 and 3 trials ($n = 1157$; 1613 PY exposure) [51], there was a numerically higher incidence ratio (IR) of herpes zoster infection among patients who received tofacitinib 5 mg twice daily (2.1; 95% CI, 0.4–6.0) and a statistically higher IR among patients who received tofacitinib 10 mg twice daily (IR, 6.6; 95% CI, 3.2–12.2) versus placebo (IR, 1.0, 95% CI, 0.0–5.4). For the overall cohort (84% received average dose of tofacitinib 10 mg twice daily), IRs were as follows: death, 0.2 (95% CI, 0.1–0.6); serious infections, 2.0 (95% CI, 1.4–2.8); opportunistic infections, 1.3 (95% CI, 0.8–2.0); herpes zoster infection, 4.1 (95% CI, 3.1–5.2); malignancy (excluding non-melanoma skin cancer), 0.7 (95% CI, 0.3–1.2); non-melanoma skin cancer, 0.7 (95% CI, 0.3–1.2); major adverse cardiovascular events, 0.2 (95% CI, 0.1–0.6); and gastrointestinal perforations, 0.2 (95% CI, 0.0–0.5). The authors concluded that, except for a dose-dependent risk of herpes zoster infection on tofacitinib, the safety of tofacitinib and biologic agents in UC appeared similar. Most cases of herpes zoster infection are uncomplicated, mild to moderate in severity, and manageable without permanent discontinuation of treatment [52, 53]. Lymphoma and solid cancers were observed in patients with rheumatoid arthritis treated with tofacitinib in controlled trials and in long-term extension studies [48]. Epstein–Barr virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications [48].

In a meta-analysis of 5 five induction and maintenance UC trials (tofacitinib, $n = 938$; placebo, $n = 282$), greater increases in total cholesterol, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were observed in subjects given tofacitinib compared with those given placebo [54]. The ratios of LDL-c to HDL-c and total cholesterol to HDL-c did not change significantly. Overall, the cholesterol changes were modest, reversible, and dose-dependent and were not associated with major adverse cardiovascular events.

Early, limited data suggest that prenatal exposure to tofacitinib is associated with pregnancy and newborn outcomes similar to those reported in the general population [55]. In the UC intervention studies, there were 11 cases of maternal exposure and 14 cases of paternal exposure before/at the time of conception or during pregnancy, resulting in 15 healthy newborns, 2 spontaneous abortions, and 2 medical terminations [55]. There were no fetal or neonatal deaths or congenital malformations. Given the limited data, the AGA IBD Parenthood Project Working Group recommended considering other options, particularly in the first trimester [32]. As data during lactation are limited, the working group advised against using tofacitinib in this setting [32].

There have been concerns that JAK inhibitors may increase the risk of thromboembolic events [56]. The A3921133 study is an ongoing, post-marketing study comparing the safety of two doses of tofacitinib (5 mg and 10 mg twice daily) and anti-TNF-α agents in patients with rheumatoid arthritis, aged 50 years or older, and at least on cardiovascular risk factor. Interim analysis showed that subjects treated with tofacitinib 10 mg twice daily had a statistically and clinically significant

increase in the rate of pulmonary embolism compared with patients treated with anti-TNF-α agents [57]. In addition, subjects in the high-dose tofacitinib arm had increased overall mortality compared to the low-dose and anti-TNF-α arms. In UC, a disorder already associated with an increased risk of thromboembolic events, maintenance doses exceeding 5 mg twice daily should be avoided.

Tofacitinib cannot be used in combination with other immunosuppressants [48]. Monitoring of blood counts, liver chemistries, and lipids is recommended. Patients starting therapy should be screened for latent tuberculosis and latent hepatitis B. Live vaccines should be avoided [48]. Colombel [52] recommended herpes zoster vaccination in all UC patients, regardless of age, before immunosuppressive therapy, including tofacitinib. In this regard, the Advisory Committee on Immunization Practice (ACIP) stated a preference for the recently approved recombinant, adjuvanted zoster vaccine (RZV; Shingrix®, GlaxoSmithKline Biologicals, Middlesex, UK) over the live virus vaccine [58]. RZV proved safe and effective in a randomized, placebo-controlled trial in renal transplant patients [59]. It should be noted that the ACIP has not made any recommendations regarding the use of RZV in immunosuppressed patients and that, presently, Shingrix has an indication only for immunocompetent individuals aged 50 years or older.

Real-World Experience

The real-world experience with tofacitinib in UC is limited. In a study from the University of Chicago, 58 patients, 93% of whom had failed anti-TNF-α therapy, completed at least 8 weeks of treatment [60]. At 8 weeks, 21 patients (36%) achieved a clinical response and 19 (33%) achieved clinical remission. Of the 26 patients followed for 12 months, 27% were in clinical, steroid-free remission. There were 12 systemic infections (mostly while on concomitant steroids) and one herpes zoster infection [60].

Predictors of Response

Predictors of response are beginning to be investigated. In the OCTAVE trials, response did not correlate with average drug concentration [49••]. Subgroup analysis showed that prior anti-TNF-α treatment or failure did not influence remission or mucosal healing at week 8 [49••]. A reduction in the baseline Mayo stool frequency subscore of ≥ 1 at days 3 and 7 predicted clinical response at week 8 with positive predictive values (PPVs) of 73.9% and 76.8%, respectively [50]. Similarly, reductions in the baseline Mayo rectal subscore of ≥ 1 at days 3 and 7 had a PPV of 65.0% and 69.9%, respectively, in predicting response at week 8 [50].

Use in Specific Clinical Settings

Due to its rapid onset of action, tofacitinib may be useful in hospitalized patients with ASUC. In a small case series, 4 patients with ASUC received tofacitinib 10 mg 3 times daily for a total of 9 doses [61]. Three of the patients also received IV methylprednisolone 60 mg daily, while the fourth received budesonide. All 4 patients had a rapid improvement in clinical symptoms and decline in CRP. Three patients achieved clinical remission. Of these 3 patients, one ultimately required elective colectomy 6 months after the hospitalization for multifocal dysplasia. The fourth patient was unable to achieve clinical remission. This patient had the highest CRP (242 mg/l) and colonic dilation despite previous treatment with IV corticosteroids for 1 week at an outside hospital. Despite these high-risk features, a rapid improvement in symptoms and CRP was observed until the dose was reduced 5 mg 2 times daily for maintenance on day 5. This dose adjustment was accompanied by a rapid rise in CRP and return of severe symptoms, necessitating urgent colectomy. No major adverse effects were observed during the induction phase of drug administration or up to 18 months of follow-up [61]. Case reports describe the successful treatment of uveitis/scleritis [62, 63] and pyoderma gangrenosum with tofacitinib [64].

Comparative Effectiveness

Studies of comparative effectiveness have used various methodologies. Propensity score–matched analysis by the VICTORY investigators showed that, compared to anti-TNF-α–treated patients, vedolizumab-treated patients had significantly higher 12-month rates of clinical remission (54% vs. 37%; HR, 1.54; 95% CI, 1.08–2.18) and endoscopic healing (50% vs. 42%; HR, 1.73; 95% CI, 1.10–2.73) [65]. Cumulative 12-month rates for steroid-free remission were numerically higher for vedolizumab-treated patients, but not statistically significant (49% vs. 38%; HR, 1.43; 95% CI, 0.79–2.60). The findings were consistent when stratified by disease extent and prior anti-TNF-α exposure. A network meta-analysis found that infliximab and vedolizumab were ranked highest as first-line agents for the induction of remission and mucosal healing of moderate–severe UC. Tofacitinib was ranked highest as a second-line agent [66].

The comparative safety of anti-TNF-α agents and vedolizumab was assessed using propensity score–matched analysis in the VICTORY cohort ($n = 872$ IBD, $n = 334$, $n = 436$ vedolizumab) [65]. Compared to anti-TNF-α–treated patients, vedolizumab-treated IBD patients had numerically lower rates of serious infections (6.9% vs. 10.1%; OR, 0.67; 95% CI, 0.41–1.07) and significantly lower rates of serious adverse events (7.1% vs. 13.1%; OR, 0.51; 95% CI, 0.32–0.81).

Among matched patients on biologic monotherapy ($n = 247$; $n = 142$ vedolizumab), vedolizumab-treated patients had numerically lower rates of serious infections (4.1% vs. 10.1%; OR, 0.37; 95% CI, 0.13–1.02) and significantly lower rates of serious adverse events (4.7% vs. 14.5%; OR, 0.29; 95% CI, 0.12–0.73). Finally, among matched patients on biologic therapy in combination with both steroids and an immunomodulator ($n = 137$; $n = 69$ vedolizumab), there were similar rates of serious infections (11.5% vs. 13.9%; OR, 0.81; 95% CI, 0.31–2.07) and serious adverse events (14% vs. 14%; OR, 0.66; 95% CI, 0.27–1.65).

The first randomized clinical trial comparing biologic agents in IBD was recently completed and is awaiting publication [67••]. VARSITY was a double-blind, double-dummy, randomized trial that compared standard doses of vedolizumab ($n = 383$) and adalimumab ($n = 386$) in patients with moderately active UC. The primary endpoint was clinical remission, defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point, at week 52. Rates of clinical remission at week 52 were 31.3% and 22.5% for the vedolizumab and adalimumab arms, respectively (absolute difference = 8.8% [2.6%, 15.0%]; $P = 0.0061$). In subgroup analysis by TNF-α status, vedolizumab was superior to adalimumab among anti-TNF-α–naïve subjects (34.2% vs. 24.3%; absolute difference = 9.9% [2.8%, 17.1%]; $P = 0.0070$) but not anti-TNF-α–experienced subjects (20.3% vs. 16.0%; absolute difference = 4.3% [− 7.7%, 16.1%]; $P = 0.49$). Similar to the results on clinical remission, vedolizumab was associated with higher rates of mucosal healing at week 52 in the overall population (39.7% vs. 27.7%; absolute difference = 12.0% [5.3%, 18.6%]; $P = 0.0005$) and in anti-TNF-α–naïve subjects (43.1% vs. 29.5%; absolute difference Δ = 13.6% [6.0%, 21.1%]; $P = 0.0005$), but not anti-TNF-α–experienced subjects (26.6% vs. 21.0%; absolute difference Δ = 5.6% [− 7.6%, 18.8%]; $P = 0.41$). Rates of clinical response became significantly different after week 6 and remained so for the duration of the trial. A limitation of the trial concerns the lack of dose optimization. Studies have demonstrated rates of adalimumab dose escalation ranging from 20% to over 50% per year [68–72], indicating that standard dosing is insufficient in many patients. As a result, guidelines have endorsed dose optimization based on biomarkers of activity and drug trough levels [4••]. Forthcoming VARSITY data on trough levels and immunogenicity may, at least in part, explain the superiority of vedolizumab over adalimumab.

New Treatment Paradigms

Two new paradigms have emerged in the treatment of UC: risk-stratified therapy [4••] and treat-to-target therapy [73••]. The standard approach that bases drug selection on current clinical activity fails to consider long-term prognosis. As an example, a patient presenting with a mild flare may actually have a high CRP and endoscopic progression from distal disease to extensive colitis. Under the standard approach, this patient would be treated with higher mesalamine doses or budesonide MMX. In contrast, using the risk-stratified approach, the patient would be deemed high-risk based on the CRP elevation and extensive involvement and would therefore be treated with steroids plus a thiopurine, an anti-TNF agent, or vedolizumab [4••]. Other markers of increased colectomy risk include age at diagnosis less than 40, history of hospitalization, prior steroid therapy, history of *Clostridium difficile* colitis or cytomegalovirus colitis, and the presence of deep ulcers [4••]. In a step towards risk stratification, both the AGA and the ACG included endoscopic severity as well as standard clinical and biochemical parameters in defining overall disease severity [4••, 5••]. The ACG stated that "selection of induction and maintenance therapies for UC should be based on disease extent, severity, and *prognosis*" [4••]. In the future, markers of drug response (and loss of response) are expected to inform treatment decisions and may replace some, but not all, clinical markers.

Symptoms and endoscopic activity can be discrepant in many patients with UC [74, 75]. The treat-to-target approach posits that clinical remission is an insufficient treatment target in so far as persistent endoscopic and histologic activity is associated with a worse prognosis, even in patients who are in clinical remission. A large body of evidence has shown that endoscopic healing, typically defined as the absence of ulcerations and erosions, is associated with higher rates of long-term clinical remission and corticosteroid-free remission, decreased hospitalizations, a lower risk of colorectal neoplasia, and a lower risk of colectomy [2, 76–81]. Similarly, histologic activity predicts clinical relapse, corticosteroid use, hospitalization, and neoplasia [77, 81, 82]. Based on these data, the STRIDE group proposed that the treatment target in UC should be clinical/patient-reported outcome remission (defined as the resolution of rectal bleeding and diarrhea/altered bowel habits) *and* endoscopic remission (defined as a Mayo endoscopic subscore of 0–1). Histological remission was proposed as an adjunctive goal [73••]. Intrinsic to this approach are optimization of initial therapy and follow-up assessment to determine whether healing has occurred. Further therapeutic actions and assessments may be necessary until the goal of healing is achieved. In its recent guidelines, the ACG suggested mucosal healing (defined as the resolution of inflammatory changes [Mayo endoscopic subscore 0 or 1]) as a treatment goal (conditional recommendation, low quality of evidence) [4••]. Prospective studies are needed comparing treat-to-target with standard care. Patient acceptance in the community setting and cost-effectiveness will also need to be assessed.

Putting It All Together

The biggest knowledge gap concerns the relative positioning of the anti-TNF agents (vedolizumab and tofacitinib) in the treatment of moderately severe UC. Several considerations enter in the selection of therapy, including the properties of the agent (rates of induction and maintenance of remission, onset of action), the disease features in the individual patient, patient preferences, and, unavoidably, the costs to the patient and the health care system (see Table 2). We make the following general suggestions for the treatment of patients with moderately severe UC:

1. For most patients, we suggest vedolizumab over adalimumab. Forthcoming VARSITY data will allow a comparison of the efficacy and safety of the two agents at different trough concentrations. It should be noted that no randomized trials have compared infliximab and vedolizumab.
2. For patients with markers of more aggressive course (such as deep ulcers or systemic manifestations) or patients who need disease control within 2–4 weeks, we suggest anti-TNF-α therapy, preferably in combination with a thiopurine.
3. For patients with anti-TNF-α–sensitive extraintestinal manifestations (such as uveitis, arthritis, and pyoderma gangrenosum), we suggest anti-TNF-α therapy, preferably in combination with a thiopurine.
4. For patients at increased risk of infection, we suggest vedolizumab.
5. We do not use tofacitinib as a first-line therapy.

Table 2 Considerations when selecting UC therapy

Drug	Patient	Health care team
Clinical remission	Predictors of prognosis 1. Short-term (severity of inflammation) 2. Long-term	Experience of nursing staff and consultants
Rapid induction of remission	Prior response to therapy (steroids, anti-TNF-α, ≥ 1 biologics)	Health care system
Durability of remission	Extraintestinal manifestations	
Predictors of response (including therapeutic drug monitoring)	Age and comorbidities	
Mucosal healing	History of infections or malignancy	
Immunogenicity	Pregnancy	
Safety profile (including infection, malignancy, and perioperative risk)	Preferences Out-of-pocket costs	

There are limited data to inform treatment decisions in patients who have failed a biologic. Many scenarios can occur, including primary failure versus loss of response, the latter due to either escape of previously controlled disease or the development of anti-drug antibodies; failure of monotherapy versus combination therapy with an immunomodulator; failure of 1 versus ≥ 2 biologics; and steroid-responsive versus steroid-refractory disease. In the absence of robust evidence, clinical judgment remains paramount. Moreover, clinicians and patients should always consider investigational studies for such patients.

Summary

Recent years have brought about several advances in the treatment of patients with UC. Vedolizumab and tofacitinib are contesting anti-TNF-α agents as a first-line therapy for moderately severe UC. A recent trial showed that vedolizumab was superior to adalimumab in achieving steroid-free clinical remission and mucosal healing at 52 weeks. We need more data on the long-term effectiveness and safety of tofacitinib. More comparative trials are urgently needed. The paradigm of drug selection based on current inflammatory activity has been challenged by the risk-stratified approach, which incorporates long-term risk as well as current burden of inflammation. The treat-to-target approach aims at improved long-term outcomes by adjusting therapy to resolve intestinal inflammation.

Compliance with Ethical Standards

Conflict of Interest Christopher M. Johnson, Catherine D. Linzay, and Themistocles Dassopoulos declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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