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CLINICAL FEATURE
REVIEW

Reviewing treatments and outcomes in the evolving landscape of ulcerative colitis

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory disease extending proximally from the rectum to varying lengths of the colon that is characterized by alternating cycles of relapse and remission. Therapeutic goals for patients with active UC include induction and maintenance of remission and improvement in quality of life, as well as mucosal healing, a clinical outcome recently recognized in treatment guidance as being equally important. Mucosal healing is associated with favorable long-term patient outcomes related to remission, surgery, hospitalization, and quality of life. Given the increasing number of newer therapies available, it is important to properly position the use of each agent within the landscape of established UC therapies, evolving therapeutic goals, and established guidelines. Extent of disease is important to consider when selecting a treatment, as is an understanding of the short- and long-term outcomes (e.g. corticosteroid-free remission, mucosal healing) associated with each treatment. The purpose of this narrative review is to provide an overview of newer therapies for the treatment of UC and how they may best fit in the evolving landscape of UC.

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Disease management; inflammatory bowel disease (IBD); mucosal healing; ulcerative colitis (UC); ulcerative colitis severity

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease affecting the colonic mucosa proximally from the rectum through to varying lengths of the colon; most patients with the condition cycle between periods of active disease and clinical remission [1]. The overall prevalence of UC in the United States has been estimated to range between 191 and 413 patients per 100,000 [2–8]. Patients with UC are most commonly classified by the extent of the disease: ulcerative proctitis (UP) is disease limited to the rectum (distal to the rectosigmoid junction); ulcerative proctosigmoiditis (UPS) affects the rectum and sigmoid colon; left-sided UC is disease extending from the rectum distal to the splenic flexure; and extensive UC (pancolitis) affects the length of the colon proximal to the splenic flexure [9–11]. The Montreal classification simplifies the categorization of extent of UC into proctitis (E1), left-sided colitis (E2), and extensive colitis (E3) [12]. The severity of UC is determined using a number of scoring instruments that initially classified patients based on clinical symptoms but have evolved over time to include endoscopic and histologic features (Table 1) [13–17]. More recently, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) rated endoscopic evidence of mucosal lesions as the most important contributor to overall UC disease severity over time [18]. Patients with UC may present with symptoms that include rectal bleeding, diarrhea, urgency, tenesmus, and abdominal pain, which impact not only quality of life and daily activities for patients but also their psychosocial well-being [1,11,19]. Estimated annual direct costs for patients with UC are significantly greater than those for patients without UC ($p < 0.0001$); hospital costs are a large part of these costs [20]. Progression of UC can occur during the course of the disease, with increasing disease severity associated with increasing disease extent [1,21].

The goals of treatment for patients with active UC include improvement in quality of life, ideally to a level prior to disease onset, and induction and maintenance of remission [22–25]. Due to the unfavorable safety profile associated with long-term use of systemic corticosteroids, corticosteroid-free remission is a desirable therapeutic goal for patients with UC [22]. Mucosal healing, considered to be a lack of inflammation or ulceration in patients with UC, has been associated with a number of favorable outcomes in patients with UC, including maintenance of remission, decreased rates of surgery and hospitalizations, and improved health-related quality of life, but it has often been overlooked as a therapeutic end point in clinical practice [22,26–31]. However, the importance of endoscopic remission as a therapeutic goal was recently recognized by the IOIBD, which recommended a composite end point of achievement of clinical remission and a Mayo endoscopic subscale score ≤1 [25]. Thus, the importance of mucosal healing for short- and long-term outcomes should not be marginalized. The aim of this narrative review is to provide an overview of therapies in the context of evolving treatment goals and established guidelines for patients with UC.

2. Methods

Studies included in this review article were identified following a comprehensive PubMed search of English-language articles

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Table 1. Instruments used in the evaluation of disease severity in clinical trials of UC.

Instrument	Components and scoring
Truelove and Witts [13]	Mild: mild diarrhea (≤4 BM/d) with only small amounts of macroscopic blood in stool; no fever; no tachycardia; no severe anemia; ESR ≤30 mm/h
	Moderate: intermediate between mild and severe disease
	Severe: severe diarrhea (≥6 BM/d) with macroscopic blood in stool; fever (i.e. mean evening temperature >99.5°F, or temperature >100°F for ≥2 of 4 d; tachycardia (i.e. mean pulse rate >90/min); anemia (i.e. Hb ≤75%); ESR >30 mm/h
Mayo DAI [14]	Stool frequency: 0 = normal number of daily stools; 1 = 1–2 stools/d more than normal; 2 = 3–4 stools/d more than normal; 3 = ≥5 stools/d more than normal
Minimum score: 0	Rectal bleeding: 0 = no blood; 1 = streaks of blood with stool less than half the time; 2 = obvious blood with stool most of the time; 3 = blood alone passed
Maximum score: 12	Endoscopic: 0 = normal or inactive disease; 1 = mild disease (erythema, decreased vascular pattern, mild friability); 2 = moderate disease (marked erythema, no vascular pattern, friability, erosions); 3 = severe disease (spontaneous bleeding, ulceration)
	PGA: 0 = normal; 1 = mild disease; 2 = moderate disease; 3 = severe disease
UCDAI [15]	Stool frequency: 0 = normal; 1 = 1–2 stools/d more than normal; 2 = 3–4 stools/d more than normal; 3 = >4 stools/d more than normal
Minimum score: 0	Rectal bleeding: 0 = none; 1 = streaks of blood; 2 = obvious blood; 3 = mostly blood
	Mucosal appearance: 0 = normal; 1 = mild friability; 2 = moderate friability; 3 = exudation, spontaneous bleeding
Maximum score: 12	Physician's rating of disease activity: 0 = normal; 1 = mild; 2 = moderate; 3 = severe
CAI by Rachmilewitz [16]	Number of weekly stools: 0 = <18; 1 = 18–35; 2 = 36–60; 3 = >60
Minimum score: 0	Blood in stool: 0 = none; 2 = little; 4 = a lot
Maximum score: 29	PGA: 0 = good; 1 = average; 2 = poor; 3 = very poor
	Abdominal pain/cramps: 0 = none; 1 = mild; 2 = moderate; 3 = severe
	Temperature (due to UC): 0 = 37–38°C; 3 = >38°C
	Extraintestinal manifestations: 3 = iritis; 3 = erythema nodosum; 3 = arthritis
	Laboratory findings: 1 = ESR >50 mm in 1st h; 2 = ESR >100 mm in 1st h; 4 = Hb <100 g/L
EI by Rachmilewitz [16]	Granulation scattering reflected light: 0 = no; 2 = yes
	Vascular pattern: 0 = normal; 1 = faded/disturbed; 2 = completely absent
Minimum score: 0	Mucosal vulnerability: 0 = none; 2 = slightly increased (contact bleeding); 4 = greatly increased (spontaneous bleeding)
Maximum score: 12	Mucosal damage: 0 = none; 2 = slight; 4 = pronounced
MMDAI [17]	Stool frequency: 0 = normal number of daily stools; 1 = 1–2 stools/d more than normal; 2 = 3–4 stools/d more than normal; 3 = ≥5 stools/d more than normal
Minimum score: 0	Rectal bleeding: 0 = no blood; 1 = streaks of blood with stool less than half the time; 2 = obvious blood with stool most of the time; 3 = blood alone passed
Maximum score: 12	Endoscopic: 0 = normal or inactive disease; 1 = mild disease; 2 = moderate disease (any degree of friability); 3 = severe disease
	PGA: 0 = normal; 1 = mild disease; 2 = moderate disease; 3 = severe disease

BM: bowel movement; CAI: clinical activity index; d: day(s); DAI: disease activity index; EI: endoscopic index; ESR: erythrocyte sedimentation rate; h: hour(s); Hb: hemoglobin; MMDAI: modified Mayo Disease Activity Index; PGA: physician's global assessment; UC: ulcerative colitis; UCDAI: ulcerative colitis disease activity index.

available through 6 March 2017. The literature search was conducted using the following key words to identify studies performed in humans: 'mild-to-moderate ulcerative colitis,' 'moderate-to-severe ulcerative colitis,' 'distal UC,' 'extensive UC,' 'ulcerative proctitis,' 'ulcerative proctosigmoiditis,' 'pancolitis,' 'rectal therapy,' 'budesonide,' 'corticosteroid,' 'immunomodulator,' 'infliximab,' 'adalimumab,' 'vedolizumab,' 'golimumab,' and 'tumor necrosis factor alpha.' References in all relevant studies and reviews were examined to identify additional articles. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the author.

3. Management of patients with UC

3.1. Considerations for treatment of UC

The choice of treatment for UC currently takes into account disease extent, disease severity, and patient concerns (e.g. extraintestinal manifestations of UC) [22,25]. Patients with distal forms of UC may only require rectal therapies, as the extent of drug distribution is limited to the distal colon, with suppositories limited to the rectum, foams extending proximally from the rectum to the sigmoid and descending colon, and enemas extending proximally from the rectum to the splenic flexure [32]. However, rectal therapies are often underused, with the greatest use being among patients with UPS. Use of rectal therapies decreases as extent of disease increases (UPS, 24.0% vs. pancolitis, 13.1%; $p = 0.001$) [33]; yet, exposure of the mucosa to drug at the site of inflammation is an advantage of rectal therapies, due to the limited distribution of rectal therapy within an affected region [22]. Finally, concerns of individual patients should factor into the choice of treatment [25]. Risks of specific adverse events may need to be considered for some patients (e.g. infections), while willingness of patients to adhere to a specific treatment regimen to achieve the therapeutic goals of remission and mucosal healing is also an important consideration for administered agents [34]. All patients with UC may require systemic medications, either with or without rectal therapies, due to the limited distribution of rectal therapy within an affected region [22].

3.2. Management of distal UC

The first-line therapy for patients with active, mild-to-moderate forms of distal UC is rectal 5-aminosalicylic acid (5-ASA) therapy [22,35]. 5-ASA suppositories and enemas induced remission or clinical improvement in a significantly larger percentage of patients compared with placebo after 4–6 weeks across studies (Table 2) [13,15,36–41], although disease severity and primary efficacy outcomes varied [15,36,37]. A *post hoc* analysis of previously published data [42] demonstrated that mucosal healing was achieved by a significantly larger percentage of patients receiving 5-ASA enemas compared with placebo after 3 weeks

Table 2. Clinical trials of 5-ASA in patients with mild-to-moderate UC.

Study and treatment(s)	Patient population	Definition of severity	Primary efficacy outcome(s)
Rectal 5-ASA			
Sutherland et al. [15] 5-ASA 4 g/60 mL enema qhs vs. PBO	Active UP, UPS, or distal UC (≥5 cm and ≤50 cm from anus)	UCDAI ≥3	• 5-ASA vs. PBO: PGA 'much improved' from baseline at Wk 6 (63% vs. 29%; $p < 0.0001$) • Decrease from baseline in UCDAI at Wk 6: 55% vs. 22% ($p < 0.0001$)
Campieri, et al. [36] 5-ASA suppository 1.5 g/d, 5-ASA suppository 1 g/d, vs. PBO	Active mild-to-moderate UP or UPS (≤20 cm from anus)	Truelove and Witts [13]	• Remission[a] at Wk 4: ○ 5-ASA 1.5 g/d, 5-ASA 1 g/d, vs. PBO: 74%, 69%, vs. 39% ($p < 0.01$ for 5-ASA groups vs. PBO)
Watanabe et al. [37] 5-ASA 1 g suppository qd vs. PBO	Active mild-to-moderate UC with rectal inflammation	UCDAI ≥4 and ≤8 with rectal mucosal score ≥2	• Endoscopic remission[b] at Wk 4: ○ 5-ASA vs. PBO: 81.5% vs. 29.7% ($p < 0.0001$)
Oral 5-ASA			
Ito et al. [39] Oral 5-ASA pH-dependent release tablet 2.4 g/d or 3.6 g/d, vs. oral 5-ASA time-dependent release tablet 2.25 g/d, vs. PBO	Active mild-to-moderate UC	• UCDAI ≥3 and ≤8 and bloody stool score ≥1 • Mild UC: UCDAI ≥3 and ≤5 • Moderate UC: UCDAI ≥6 and ≤8	• Decrease from baseline in UCDAI at Wk 8 (primary end point): ○ 5-ASA 2.4 g, 5-ASA 3.6 g, 5-ASA 2.25 g, vs. PBO (1.5, 2.9, 1.3, vs. 0.3) • Remission[c] at Wk 8 (secondary end point): ○ 30.3%, 45.3%, 28.6%, vs. 9.4%
Flourié et al. [38] Oral 5-ASA 4 g qd vs. oral 5-ASA 2 g bid	Active mild-to-moderate UC extending beyond the rectum (≥12–18 cm from anorectal junction)	UCDAI ≥3 and ≤8	• Clinical and endoscopic remission[d] at Wk 8: ○ 5-ASA qd vs. 5-ASA bid: 52.1% vs. 41.8% ($p = 0.1$)
Oral and rectal 5-ASA			
Safdi et al. [40] 5-ASA 4 g rectal enema qhs, oral 5-ASA 2.4 g/d (800 mg tablets tid), or 5-ASA 4 g enema qhs plus oral 5-ASA 2.4 g/d (combination tx)	Active mild-to-moderate distal UC (≥5 cm and ≤50 cm from anal verge)	UCDAI ≥4 and ≤10	• Decrease from baseline in mean UCDAI at Wk 6: ○ 5-ASA enema, oral 5-ASA, or combination tx: 4.4, 3.9, or 5.2, respectively (p = NS for all comparisons)
Marteau et al. [41] Oral 5-ASA 1 g bid for 8 wk plus 5-ASA enema 1 g/100 mL qhs for first 4 wk (combination tx), or oral 5-ASA 1 g bid for 8 wk plus PBO enema for first 4 wk	Active extensive mild-to-moderate UC (beyond the splenic flexure by colonoscopy)	• UCDAI ≥3 and ≤8 • Mild UC: UCDAI ≥3 and ≤5 • Moderate UC: UCDAI ≥6 and ≤8	• Remission[e] at Wk 4: ○ Oral 5-ASA plus 5-ASA enema vs. oral 5-ASA plus PBO enema: 44% vs. 34% ($p = 0.3$)

[a]Remission defined as the absence of symptoms, with ≤2 BM/d without visible blood in stool.
[b]Endoscopic remission defined as rectal mucosal score ≤1 at site of rectal inflammation.
[c]Remission defined as UCDAI ≤2 and bloody stool subscore of 0.
[d]Remission defined as UCDAI ≤1.
[e]Remission defined as UCDAI <2.
5-ASA: 5-aminosalicylate; bid: twice daily; BM: bowel movement; d: day(s); NS: not significant; PBO: placebo; PGA: physician's global assessment; qd: once daily; qhs: once daily at bedtime; tid: 3 times daily; tx: treatment; UC: ulcerative colitis; UCDAI: ulcerative colitis disease activity index; UP: ulcerative proctitis; UPS: ulcerative proctosigmoiditis; wk: week(s).

(25.0% vs. 7.8%, respectively; $p < 0.005$) and 6 weeks (42.1% vs. 19.5%, respectively; $p < 0.005$).

Clinical trials of rectal 5-ASA, oral 5-ASA, or combination of rectal and oral 5-ASA therapies in patients with distal forms of UC have differed not only in the patient populations examined (i.e. according to definitions of distal UC) but also in definitions of disease severity used and primary efficacy outcomes selected (Table 2). Rectal 5-ASA therapies have demonstrated efficacy in patients with UC but are often underutilized, according to one 2014 analysis of data derived from a larger cohort study, with 23.3% of patients with UP using rectal 5-ASAs, compared with rectal 5-ASA use in 5.0%, 4.3%, and 4.7% of patients with UPS, left-sided UC, or pancolitis, respectively [33]. Conversely, use of oral 5-ASAs was much greater than that of rectal 5-ASAs, with use of oral 5-ASAs seen in 28.7%, 39.7%, 35.0%, and 39.7% of patients with UP, UPS, left-sided UC, or pancolitis.

A number of oral 5-ASA formulations have been developed; they are characterized by differences in time to absorption and duration of release of 5-ASA in the colon [43]. It is worth noting that efficacy of specific formulations (i.e. pH-dependent release, time-release) has been associated with disease extent and severity (Table 2). A pH-dependent oral 5-ASA formulation was shown to have significantly greater efficacy (i.e. decrease from baseline measured by the UC disease activity index (UCDAI) to Week 8) compared with placebo in patients with distal UC (i.e. 'proctitis-type'); there was no difference in efficacy between the time-dependent release of oral 5-ASA and placebo in patients with distal UC. Similarly, pH-dependent oral 5-ASA 2.4-g and 3.6-g formulations had greater efficacy compared with placebo in patients with mild UC (i.e. UCDAI ≥3 and ≤5); in patients with moderate UC (i.e. UCDAI ≥6 and ≤8), only pH-dependent oral 5-ASA 3.6 g had greater efficacy versus placebo [39], meaning that extent and severity of UC may be considered when prescribing an oral 5-ASA for the induction of remission of mild-to-moderate UC. However, meta-analyses of oral 5-ASAs for the induction of remission of UC found no differences in efficacy between 5-ASA formulations [44,45].

While 5-ASA monotherapy has demonstrated efficacy in patients, combination treatment with rectal and oral 5-ASAs had greater efficacy than 5-ASA monotherapy in studies of patients with distal forms of mild-to-moderate UC (Table 2) and is recommended for patients with mild-to-moderate left-sided UC [22,35,40,41]. However, definitions of mild-to-

moderate UC differed among these studies. Indeed, results of a meta-analysis of four randomized, controlled studies found that induction of remission of mild-to-moderate UC was not achieved by 55.1% and 37.3% of patients receiving oral 5-ASAs alone or a combination of oral and rectal 5-ASAs, respectively [46].

Rectal corticosteroids are also recommended for patients with mild-to-moderate distal UC [22], but as second-line therapy in patients refractory to rectal 5-ASAs [35]. Oral and rectal corticosteroids have demonstrated efficacy for the induction of remission of mild-to-moderate UC [47] but are not recommended for long-term maintenance of remission of UC [48]. Rectal administration of conventional corticosteroids was associated with decreased cortisol concentrations compared with rectal budesonide [49] and may increase the risk of cumulative systemic exposure to corticosteroids [48].

Second-generation corticosteroids (budesonide, beclomethasone dipropionate) have high first-pass hepatic metabolism and are associated with fewer corticosteroid-related adverse effects than conventional corticosteroids [50–57]. Budesonide foam, a formulation approved in 2014 for the induction of remission of active, mild-to-moderate distal UC, has a maximal spread to 40 cm (mean, 25.4 cm) proximal from the rectum to the descending colon [58,59]. Budesonide foam has demonstrated efficacy in a number of clinical studies, inducing remission in patients with UP, UPS, or distal UC after 4–8 weeks of treatment (Table 3) [16,17,53,60–64]. Disease severity was determined using both symptom- and endoscopic-based disease activity instruments, although patient inclusion criteria varied across the studies [17,53,60]. In two randomized, placebo-controlled studies, a significantly greater percentage of patients receiving budesonide foam achieved remission (i.e. Mayo endoscopic subscale score ≤1, Mayo rectal bleeding subscale score of 0, and improvement or no change from baseline in the Mayo stool frequency subscale score) or mucosal healing (i.e. Mayo endoscopic subscale score ≤1) compared with placebo at Week 6 ($p < 0.0001$ and $p = 0.0002$, respectively) [17]. Current guidelines make no specific recommendations for or against the use of budesonide foam for the induction of remission of distal UC, but current opinion suggests that budesonide foam should be considered as second-line therapy for patients with UP refractory to treatment with rectal 5-ASA [65].

3.3. Oral 5-ASA and corticosteroid therapies for UC

Oral 5-ASA is currently recommended as first-line therapy for patients with active, mild-to-moderate extensive UC [22,35]. In a study of patients with mild-to-moderate UC (i.e. UCDAI ≥3 and ≤8) and disease extending ≥12–18 in from the anorectal junction (83% of patients with distal or left-sided UC), once-daily dosing of oral 5-ASA 4 g induced clinical and endoscopic remission (i.e. UCDAI ≤1) as effectively as twice-daily dosing of oral 5-ASA 2 g after 8 weeks [38]. However, a significantly greater percentage of patients receiving once-daily 5-ASA achieved improvement from baseline in the UCDAI at Week 8, compared with patients receiving twice-daily 5-ASA (92% vs. 79%, respectively; $p = 0.01$). Mucosal healing (i.e. UCDAI endoscopic subscale score ≤1) was achieved by a significantly greater percentage of patients receiving once-daily versus twice-daily oral 5-ASA dosing (87.5% vs. 71.1%, respectively; $p = 0.007$). Thus, the efficacy of once-daily oral 5-ASA dosing supports the use of this more convenient dosing regimen in patients with active, mild-to-moderate UC, which is thought to improve adherence to therapy in patients with UC [66].

Oral corticosteroids are recommended for patients refractory to treatment with oral 5-ASA medications [22,35]. While systemic oral corticosteroids (e.g. prednisone) are efficacious for the induction of remission in patients with UC [67,68], their side effect profile and lack of long-term mucosal healing data render them an ineffective maintenance strategy [22]. The oral, once-daily, extended-release formulation of budesonide, budesonide with multimatrix technology (MMX), was introduced after the publication of earlier guidelines [22,35]. Budesonide MMX, which is indicated for the induction of remission of active, mild-to-moderate UC [69], utilizes MMX to deliver the drug throughout the length of the colon [70]. Use of budesonide MMX was recently proposed for patients with active, mild-to-moderate UC who are refractory to or have relapsed following first-line treatment with 5-ASA, but before the introduction of systemic corticosteroids [71]; indeed, budesonide MMX induced clinical and endoscopic remission (based on the UCDAI) after 8 weeks in patients with mild-to-moderate UC in both the Colonic Release Budesonide (CORE) I and CORE II studies (Table 3) [61,62]. Budesonide MMX also induced remission (as measured by clinical activity index (CAI) score) or improved CAI scores ≥50% from baseline after 4 weeks in patients with moderate left-sided UC, although the findings of this study did not reach statistical significance [63]. In the CORE I study, budesonide MMX 9 mg was associated with endoscopic improvement (i.e. improvement from baseline in UCDAI mucosal appearance subscale score ≥1) in a greater percentage of patients compared with placebo at Week 8 (41.5% vs. 33.1%, respectively) [61]. These results are comparable with those observed in the CORE II study, which reported that endoscopic improvement, by the same definition used in the CORE I study, occurred in 42.2% and 31.5% of patients receiving budesonide MMX 9 mg or placebo, respectively, at Week 8 [62]. Thus, while long-term effects of budesonide MMX on mucosal healing are currently unknown, this second-generation oral corticosteroid may be a promising alternative for patients with mild-to-moderate, extensive UC who would otherwise receive systemic corticosteroids.

Oral beclomethasone dipropionate is a second-generation corticosteroid with limited systemic activity that is released throughout the colon [72,73]. A meta-analysis compared the efficacy and safety of at least 4 weeks of treatment with oral beclomethasone dipropionate with oral prednisone or oral 5-ASAs in five randomized, controlled studies of patients with mild-to-moderate left-sided or extensive UC [72]. The odds of achieving clinical response, as defined by each independent study, were significantly greater with oral beclomethasone dipropionate compared with oral prednisone or oral 5-ASAs (65.6% vs. 60.0%, respectively; odds ratio (OR), 1.41; 95% confidence interval (CI), 1.03–1.93; $p = 0.03$); no significant differences were observed for clinical remission, as

Table 3. Clinical trials with budesonide in patients with mild-to-moderate UC.

Study and treatment(s)	Patient population	Definition of severity	Primary efficacy outcome(s)
Budesonide foam			
Hammond et al. [53] Budesonide foam 2 mg/50 mL vs. betamethasone enema 5 mg/100 mL bid for 2 wk, then qhs for 2 wk	Active distal UC	Pts without prior tx: CAI >8 and EI >6; Pts refractory to 5-ASA: CAI >5; Pts refractory to corticosteroid tx (prednisolone or equivalent, <20 mg for <2 wk): CAI ≥5 and EI >6	• Remission[a] at Wk 4: ○ Budesonide foam vs. betamethasone enema: 40.9% vs. 81.3%
Gross et al. [60] Budesonide foam 2 mg/25 mL vs. budesonide enema 2 mg/100 mL	Active UP or UPS (up to 40 cm)	CAI >4 and EI ≥4, by Rachmilewitz [16]	• Remission[a] at Wk 4: ○ Budesonide foam vs. budesonide enema: 65.7% vs. 59.5%
Sandborn et al. [17] Budesonide rectal foam 2 mg/25 mL vs. PBO bid for 2 wk, then qd for 4 wk	Active UP or UPS (≥5 cm and ≤40 cm from anal verge)	MMDAI ≥5 and ≤10, with subscores ≥2 for endoscopy and rectal bleeding	• Remission[b] at Wk 6: ○ Budesonide foam vs. PBO: 41.2% vs. 24.0% ($p < 0.0001$)
Naganuma et al. [64] Budesonide rectal foam 2 mg/25 mL qd or bid vs. PBO for 6 wk	Active UP or UPS (from rectum to sigmoid colon)	MMDAI subscores of 2 for endoscopy, 1 or 2 for rectal bleeding, and ≤2 for stool frequency	• Complete mucosal healing at Wk 6[c]: ○ Budesonide foam qd or bid vs. PBO: 23.6% or 46.6% vs. 5.6% ($p = 0.0156$ or $p < 0.0001$, respectively) • Clinical remission[d]: ○ Budesonide foam qd or bid vs. PBO: 50.9% or 48.2% vs. 20.4% ($p = 0.0015$ or $p = 0.0029$, respectively)
Budesonide MMX			
D'Haens et al. [63] Budesonide MMX 9 mg vs. PBO	Active moderate left-sided UC (≥15 cm from anal verge to the splenic flexure)	CAI <14 [16]	• Clinical improvement[e] at Wk 4: ○ Budesonide MMX 9 mg vs. PBO: 47.1% vs. 33.3% ($p = 0.1$)
Sandborn et al. [61] Budesonide MMX 9 mg qd, budesonide MMX 6 mg qd, 5-ASA 800 mg tid, or PBO for 8 wk	Active mild-to-moderate UC	UCDAI ≥4 and ≤10, with histologic confirmation of UC performed by central reading	• Combined clinical and endoscopic remission[f] at Wk 8: ○ Budesonide MMX 9 mg, budesonide MMX 6 mg, 5-ASA, vs. PBO: 17.9%, 13.2%, 12.1%, vs. 7.4% ($p = 0.01$, $p = 0.1$, and $p = 0.2$, vs. PBO, respectively)
Travis et al. [62] Budesonide MMX 9 mg qd, budesonide MMX 6 mg qd, budesonide-CIR 9 mg/d, or PBO for 8 wk	Active mild-to-moderate UC	UCDAI ≥4 and ≤10, with histologic confirmation of UC performed by central reading	• Combined clinical and endoscopic remission[f] at Wk 8: ○ Budesonide MMX 9 mg, budesonide MMX 6 mg, budesonide-CIR, vs. PBO: 17.4%, 8.3%, 12.6%, vs. 4.5% ($p = 0.005$, p = NS, and $p = 0.048$, vs. PBO, respectively)

[a]Remission defined as CAI ≤4.
[b]Remission defined as MMDAI endoscopic subscale score ≤1, rectal bleeding subscale score = 0, and improvement or no change from baseline in stool frequency subscale score.
[c]MMDAI endoscopy subscore of 0.
[d]MMDAI endoscopy subscore ≤1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or decrease from baseline ≥1.
[e]Clinical improvement defined as remission (CAI ≤4), or decrease from baseline ≥50% in CAI.
[f]Remission defined as UCDAI score ≤1, with rectal bleeding and stool frequency subscores of 0, no mucosal friability on colonoscopy, and a decrease from baseline ≥1 in EI score.
5-ASA: 5-aminosalicylate; bid: twice daily; CAI: clinical activity index; CIR: controlled ileal release; EI: endoscopic index; MMDAI: modified Mayo Disease Activity Index; MMX: multi-matrix; NS: not significant; PBO: placebo; pts: patients; qd: once daily; tid: 3 times daily; tx: treatment; UC: ulcerative colitis; UCDAI: ulcerative colitis disease activity index; UP: ulcerative proctitis; UPS: ulcerative proctosigmoiditis; wk: week(s).

defined in the individual studies (OR, 1.30; 95% CI, 0.76–2.23; $p = 0.34$) [72]. Clinical response was significantly more likely after 4 weeks with oral beclomethasone dipropionate than oral 5-ASAs (OR, 1.86; 95% CI, 1.23–2.82; $p = 0.003$) [72]. There were no differences in safety between oral beclomethasone dipropionate and oral 5-ASAs (OR, 0.55; 95% CI, 0.24–1.27; $p = 0.2$) [72]. Thus, results of this meta-analysis demonstrated that oral beclomethasone had similar, or improved, efficacy and safety compared with oral prednisone and 5-ASAs [72,74].

3.4. Immunomodulators

The thiopurines azathioprine and its metabolite, mercaptopurine (MP), are immunomodulators that have a long history of use for the treatment of UC [75]. According to the guidelines from the American College of Gastroenterology, thiopurines are recommended for patients with more moderate UC who fail to respond to corticosteroids but who do not require intravenous (IV) treatment, although this may not reflect clinical practice [22]. Azathioprine has demonstrated efficacy for the induction and maintenance of remission (defined as absence of disease activity according to Truelove and Witts [13]) of UC in patients dependent on or resistant to corticosteroids [76]. Further, long-term treatment with azathioprine (>5 years) was shown to be well tolerated and efficacious for the treatment of patients with UC [75]. Of patients receiving azathioprine for >5 years, 85.9% were considered to have achieved clinical benefit (defined as being 'well' by physician's global assessment (PGA) and complete withdrawal of oral corticosteroids) [75]. A Cochrane systematic review of six studies found that azathioprine had greater efficacy than placebo for maintenance of remission of UC [77]. However, the findings of this systematic review were limited by the lack of inclusion of

high-quality studies and a small patient number (n = 286). Some patients with UC or Crohn's disease (CD) receiving thiopurines may have altered metabolism of the drugs, leading to adverse effects that may result in discontinuation of treatment [78]. Safety concerns with thiopurines that are estimated to affect approximately 20% of patients include myelotoxicity, hepatotoxicity, pancreatitis, and nausea [79,80]. In one follow-up study, 17% of patients discontinued treatment with thiopurines due to adverse events [80].

Methotrexate has long been used to treat patients with inflammatory disorders (e.g. rheumatoid arthritis (RA)) [81]. However, a Cochrane systematic review of two studies found that methotrexate did not have improved efficacy for the induction of remission (defined as Mayo score ≤3 and withdrawal from corticosteroids) of UC compared with placebo or active comparators (e.g. MP, 5-ASA) [82]. Similarly, the efficacy of parenteral methotrexate for the induction of remission of steroid-dependent UC was found to be comparable with that of placebo in the randomized, double-blind Comparison of Methotrexate vs Placebo in Corticosteroid-Dependent Ulcerative Colitis study [81]. A comparable percentage of patients achieved corticosteroid-free remission (primary end point; defined as a total Mayo score ≤2, with no subscale score >1, complete withdrawal of corticosteroids, no use of immunosuppressants or tumor necrosis factor-alpha (TNF-α) antagonists, or colectomy) with parenteral methotrexate and placebo after 16 weeks (31.7% vs. 19.6%, respectively; p = 0.2) [81]. However, a significantly greater percentage of patients receiving methotrexate achieved clinical remission (defined as a total Mayo score ≤2, with no subscale score >1, and no use of corticosteroids) compared with placebo after 16 weeks (41.7% vs. 23.5%, respectively; p = 0.04). Although the efficacy of parenteral methotrexate for the maintenance of remission of UC is currently under evaluation in the Methotrexate Response in Treatment of UC study [81], the findings of a Cochrane systematic review of three studies examining the efficacy of methotrexate for the maintenance of remission of UC for up to 76 weeks were inconclusive [83].

3.5. TNF-α antagonists

The three TNF-α antagonists currently approved by the US Food and Drug Administration for the treatment of patients with moderate-to-severe UC are infliximab, adalimumab, and golimumab [84]. While the determinants of response to TNF-α antagonists in patients with UC have not been fully elucidated, these agents bind TNF-α, preventing the interaction between TNF-α and its receptor and inhibiting downstream proinflammatory signaling pathways involved in apoptosis of gastrointestinal epithelial cells and decreased mucosal barrier function [84,85]. However, one preclinical study suggested that the cytokine interleukin 22 may play a role in the efficacy of TNF-α antagonists in UC [86]. TNF-α antagonists are recommended for patients who are refractory to corticosteroids or thiopurines or dependent on corticosteroids despite treatment with thiopurines (Table 4) [22,35,87–94].

The SUCCESS study examined the efficacy and safety of infliximab, azathioprine, or the combination of infliximab and azathioprine in patients with moderate-to-severe UC who were TNF-α antagonist naive (Table 4) [94]. The percentage of patients achieving corticosteroid-free remission (defined as total Mayo score ≤2, with no subscale score >1, and no use of corticosteroids) after 16 weeks was significantly greater with infliximab and azathioprine combination therapy than with infliximab or azathioprine treatment alone (39.7% vs. 22.1% or 23.7%, respectively; p = 0.02 or p = 0.03, respectively) [94]. Further, a greater percentage of patients receiving infliximab and azathioprine combination therapy achieved mucosal healing (Mayo endoscopic subscale score ≤1; 62.8%), compared with azathioprine monotherapy (36.8%; p = 0.001) or infliximab monotherapy (54.6%; p = 0.3). Treatment with either the combination of infliximab and azathioprine, or each agent alone, was well tolerated by patients. Antidrug antibody development may occur in patients receiving TNF-α antagonists, increasing drug clearance and leading to a decrease in the duration of response [95,96]. Concomitant treatment with immunomodulators (e.g. azathioprine, MP, methotrexate) may counter the development of antidrug antibodies, as patients receiving combination therapy had a decreased concentration of antibodies generated against TNF-α antagonists [96,97]. Indeed, antidrug antibody formation was reported in 19% and 3% of patients receiving infliximab monotherapy, or infliximab and azathioprine combination therapy, respectively, in the SUCCESS study [94].

In a number of clinical studies, some patients with moderate-to-severe UC reporting baseline corticosteroid use were able to discontinue corticosteroids following treatment with TNF-α antagonists, an important goal of treatment for patients with UC [22]. In the Active Ulcerative Colitis (ACT) 1 and ACT 2 studies, a greater percentage of patients with moderate-to-severe UC with baseline corticosteroid use achieved remission and discontinued corticosteroid treatment after 30 weeks with infliximab compared with placebo [93]. In these studies, the rate of corticosteroid-free symptomatic remission (defined as a Mayo stool frequency subscale score ≤1 and a rectal bleeding subscale score = 0) was significantly greater in patients with lower Mayo endoscopic subscale scores after 8-week infliximab treatment compared with patients with higher endoscopy scores at Week 30 (Mayo endoscopic subscale score of 0, 46.0%; 1, 34.0%; 2, 11.0%; 3, 6.5%; p < 0.0001) and Week 54 (Mayo endoscopic subscale score of 0, 47.0%; 1, 35.0%; 2, 5.3%; 3, 5.3%; p < 0.0001) of follow-up [28]. Further, most patients with Mayo endoscopic subscale scores of 0 (95%) or 1 (95%) after infliximab treatment had not undergone a colectomy at Week 54 [28]. Among responders to infliximab in the ACT 1 and ACT 2 long-term extension studies, 13 of the 20 patients (65%) remaining had no disease (PGA score of 0), and improvement in health-related quality of life was maintained for up to 3 years; endoscopic outcomes were not evaluated in these long-term extension studies [98]. Results of a retrospective cohort study of patients with moderate-to-severe UC receiving infliximab maintenance treatment found that patients achieving complete remission (i.e. partial Mayo score of 0, with or without corticosteroid use) with induction therapy were more likely to achieve corticosteroid-free remission (i.e. partial Mayo score of 0, without use of systemic corticosteroids) after 1 year, compared with patients not achieving complete remission with induction therapy (68.3% vs. 28.2%, respectively; p = 0.001; OR, 4.5; 95% CI, 1.8–11.5) [99]. Thus, patients with early response to infliximab may be more likely to achieve favorable long-term outcomes with

Table 4. Clinical trials of TNF-α antagonists in patients with moderate-to-severe UC.

Study and treatment(s)	Patient population and definition of severity	Efficacy outcomes			
		Remission	Response	Mucosal healing	Rectal bleeding
Adalimumab					
Induction of remission					
ULTRA 1 [87] Adalimumab 160 mg SC at Wk 0, 80 mg at Wk 2, then 40 mg at Wk 4 and 6 (160/80); adalimumab 80 mg at Wk 0, then 40 mg at Wk 2, 4, and 6 (80/40); vs. PBO	Active moderate-to-severe UC • Mayo score ≥6 and ≤12, with endoscopic subscale score of 2 or 3	Wk 8[a] – adalimumab 160/80, 80/40, vs. PBO: 18.5%, 10%, vs. 9.2% (adalimumab 160/80 vs. PBO, $p = 0.03$)	Wk 8[b] – adalimumab 160/80, 80/40, vs. PBO: 54.6%, 51.5%, vs. 44.6%	Wk 8[c] – adalimumab 160/80, 80/40, vs. PBO: 46.9%, 37.7%, vs. 41.5%	Wk 8[d] – adalimumab 160/80, 80/40, vs. PBO: 77.7%, 70%, vs. 66.2% (adalimumab 160/80 vs. PBO, $p = 0.04$)
ULTRA 2 [88] Adalimumab 160 mg SC at Wk 0, 80 mg at Wk 2, then 40 mg eow at Wk 4, vs. PBO for 52 wk	Moderate-to-severe UC • Mayo score ≥6 and ≤12, with endoscopic subscale score of ≥2	Wk 8[a] – adalimumab vs. PBO: 16.5% vs. 9.3% ($p = 0.02$) Wk 52[a] – 17.3% vs. 8.5% ($p = 0.004$)	Wk 8[b] – adalimumab vs. PBO: 50.4% vs. 34.6% ($p < 0.001$) Wk 52[b] – 30.2% vs. 18.3% ($p = 0.002$)	Wk 8[c] – adalimumab vs. PBO: 41.1% vs. 31.7% ($p = 0.03$) Wk 52[c] – 25% vs. 15.4% ($p = 0.009$)	Not reported
Maintenance of remission					
ULTRA 1, 2, and 3 [89] ULTRA 3: Pts receiving OL adalimumab 40 mg eow or wkly in ULTRA 1 or 2 continued same dosing; pts receiving blinded adalimumab or PBO in ULTRA 2 received adalimumab 40 mg eow	Active moderate-to-severe UC • Mayo score ≥6 and ≤12, with endoscopic subscale score of ≥2, despite tx with oral corticosteroids and/or immunosuppressants (prior or current use)	Y 4[e]: 24.7% Wk 52[f]: 40.3% Wk 52[g]: 27.4% Wk 196[g]: 39.7%	Not reported	Wk 52[c]: 42.3% Wk 196[c]: 27.7%	Not reported
ULTRA 2 [90] Responders at Wk 8 who escalated to OL wkly dosing for 52 wk	Moderate-to-severe UC • Mayo score ≥6 and ≤12, with endoscopic subscale score of ≥2	Wk 52[a] – Responders: 20%, vs. nonresponders: 2.1% Wk 52[g] – Responders: 17.6%, vs. nonresponders: 0%	Wk 52[b] – Responders: 45%, vs. nonresponders: 25%	Wk 52[c] – Responders: 45%, vs. nonresponders: 29.2%	Not reported
Golimumab					
Induction of remission					
PURSUIT-SC [91] Golimumab 400 mg SC at Wk 0, then 200 mg SC at Wk 2 (400/200); golimumab 200 mg SC at Wk 0, then 100 mg SC at Wk 2 (200/100); or PBO	Moderate-to-severe UC (excluding pts with UC limited to 20 cm of colon (i.e. UP)) • Mayo score ≥6 and ≤12, with endoscopic subscale score ≥2	Wk 6[h] – golimumab 400/200, 200/100, vs. PBO: 17.9%, 17.8%, vs. 6.4% ($p < 0.0001$ for both groups vs. PBO)	Wk 6[b] – golimumab 400/200, 200/100, vs. PBO: 54.9%, 51.0%, vs. 30.3% ($p < 0.0001$ for both groups vs. PBO)	Wk 6[c] – golimumab 400/200, 200/100, vs. PBO: 45.1%, 42.3%, vs. 28.7% (400/200 vs. PBO, $p < 0.0001$; 200/100 vs. PBO, $p = 0.001$)	Not reported
Maintenance of remission					
PURSUIT-M [92] Golimumab 100 mg or 50 mg every 4 wk for 52 wk, or PBO	Moderate-to-severe UC • Mayo score ≥6 and ≤12, with endoscopic subscale score ≥2	Wk 30 and 54[h] – golimumab 100 mg, 50 mg, vs. PBO: 27.8%, 23.2%, vs. 15.6% ($p = 0.004$ and p = NS vs. PBO, respectively)	Wk 54[b] – golimumab 100 mg, 50 mg, vs. PBO: 49.7%, 47.0%, vs. 31.2% ($p < 0.001$ and $p = 0.01$ vs. PBO, respectively)	Wk 30 and 54[c] – golimumab 100 mg, 50 mg, vs. PBO: 42.4%, 41.7%, vs. 26.6% ($p = 0.002$ and $p = 0.01$ vs. PBO, respectively)	Not reported
Infliximab					
Induction of remission					
ACT 1 and ACT 2 [93] Infliximab 10 mg/kg or 5 mg/kg IV at Wk 0, 2, and 6, then every 8 wk for 46 wk (ACT 1) or 22 wk (ACT 2), or PBO	Active moderate-to-severe UC • Mayo score ≥6 and ≤12, with endoscopic subscale score ≥2	Wk 8[a] – ACT 1: infliximab 10 mg/kg, 5 mg/kg, vs. PBO: 32%, 38.8%, vs. 14.9% ($p = 0.002$ (10 mg/kg infliximab vs. PBO) and $p = 0.001$ (5 mg/kg infliximab vs. PBO)) ACT 2: 27.5%, 33.9%, vs. 5.7% ($p < 0.001$ for both vs. PBO)	Wk 8[b] – ACT 1: infliximab 10 mg/kg, 5 mg/kg, vs. PBO: 61.5%, 69.4%, vs. 37.2% ($p < 0.001$ for both vs. PBO) ACT 2: 69.2%, 64.5%, vs. 29.3% ($p < 0.001$ for both vs. PBO)	Wk 8[c] – ACT 1: infliximab 10 mg/kg, 5 mg/kg, vs. PBO: 59%, 62%, vs. 33.9% ($p < 0.001$ for both vs. PBO) ACT 2: 61.7%, 60.3%, vs. 30.9% ($p < 0.001$ for both vs. PBO)	Not reported

(*Continued*)

Table 4. (Continued).

Study and treatment(s)	Patient population and definition of severity	Efficacy outcomes			
		Remission	Response	Mucosal healing	Rectal bleeding
Infliximab					
Maintenance of remission SUCCESS [94] Infliximab 5 mg/kg IV at Wk 0, 2, 6, and 14; azathioprine 2.5 mg/kg capsules qd; or infliximab/azathioprine combination tx, for 16 wk	Active moderate-to-severe UC • Moderate UC: Mayo score ≥6 and ≤8 • Severe UC: Mayo score ≥9 and ≤12	Wk 16[g] – infliximab, azathioprine, vs. combination tx: 22.1%, 23.7%, vs. 39.7% (infliximab vs. combination, $p = 0.02$; azathioprine vs. combination, $p = 0.03$)	Wk 16[i] – infliximab, azathioprine, vs. combination tx: 68.8%, 50%, vs. 76.9% (infliximab vs. combination, $p = 0.5$; azathioprine vs. combination, $p = 0.001$)	Wk 16[c] – infliximab, azathioprine, vs. combination tx: 54.6%, 36.8%, vs. 62.8% (infliximab vs. combination, $p = 0.3$; azathioprine vs. combination, $p = 0.001$)	Not reported

[a]Remission defined as Mayo score ≤2, with no individual subscale score >1.
[b]Response defined as a decrease from baseline in Mayo score ≥3 and ≥30%, with either a decrease in rectal bleeding subscale score ≥1 or a rectal bleeding subscale score ≤1.
[c]Mucosal healing defined as Mayo endoscopic subscale score ≤1.
[d]Mayo rectal bleeding subscale score ≤1.
[e]Remission defined as partial Mayo score ≤2, with no individual subscale score >1.
[f]Inflammatory Bowel Disease Questionnaire score ≥170.
[g]Mayo score ≤2, with no individual subscale score >1, and discontinuation of corticosteroid use.
[h]Remission defined as Mayo score ≤2, with no individual subscale score >1.
[i]Response defined as a decrease from baseline in Mayo score ≥3 and ≥30%.
ACT 1: Active Ulcerative Colitis Trial 1; ACT 2: Active Ulcerative Colitis Trial 2; D: day(s); eow: every other week; IV: intravenous; NS: not significant; OL: open-label; PBO: placebo; pts: patients; PURSUIT-M: Program of UC Research Studies Utilizing an Investigational Treatment-Maintenance; PURSUIT-SC: Program of UC Research Studies Utilizing an Investigational Treatment-SC; qd: once daily; SC: subcutaneous; SUCCESS: trial comparing infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis; TNF: tumor necrosis factor; tx: treatment; UC: ulcerative colitis; ULTRA 1, 2, and 3: Ulcerative Colitis Long-Term Remission and Maintenance With Adalimumab; UP: ulcerative proctitis; wk week(s); wkly: weekly, Y: year.

treatment (e.g. corticosteroid-free remission), although this particular study did not assess mucosal healing, a major limitation acknowledged by the authors.

In the Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab 2 trial, 17.6% of patients with moderate-to-severe UC who increased the frequency of adalimumab dosing from every other week to weekly achieved corticosteroid-free remission at Week 52 [90]. Further, in this study, 45.0% and 29.2% of patients with or without response to adalimumab at Week 8, respectively, achieved mucosal healing (i.e. Mayo endoscopic subscale score ≤1) at Week 52, suggesting that early response to treatment may be an important factor for achieving endoscopic remission at 1 year. However, it should be noted that a significantly greater percentage of Week 8 responders than nonresponders had baseline use of oral corticosteroids ($p \leq 0.02$). In the Program of Ulcerative Colitis Research Studies Utilizing an Investigational Tretment-Maintenance (PURSUIT-M) study, of the approximately 54% of patients with moderate-to-severe UC in remission, 23.2% of patients receiving golimumab 100 mg, 28.2% receiving golimumab 50 mg, and 18.4% receiving placebo, maintained corticosteroid-free clinical remission after 54 weeks; all of these patients also received concomitant baseline corticosteroids [92]. Further, mucosal healing (i.e. Mayo endoscopic subscale score ≤1) in this maintenance study was achieved by 42.4% and 41.7% of patients receiving golimumab 100 mg or 50 mg, respectively, compared with 26.6% of patients receiving placebo at both Weeks 30 and 54 ($p = 0.002$ and $p = 0.01$, respectively). More recently, 86% of patients from PURSUIT-M who continued golimumab therapy for up to 104 weeks in a long-term extension study maintained clinical response (i.e. inactive or mild disease); further, 88.5% of patients in the long-term extension study maintained corticosteroid-free remission at Week 104 [100]. Although a number of patients achieved corticosteroid-free remission and mucosal healing with TNF-α antagonists, it should be noted that this important outcome was not achieved by the majority of patients evaluated in these studies; thus, other treatment options may need to be considered in the long term [35].

3.6. Anti-integrin antibodies

Adhesion molecules expressed on gut endothelial cells play a key role in the recruitment of lymphocytes from blood to the gut [101]. The α4β7 integrins expressed on lymphocytes adhere to ligands on the endothelial surface, thus allowing for migration of lymphocytes to sites of inflammation. Anti-integrin antibodies, including vedolizumab, inhibit the migration of lymphocytes across the mucosal barrier by targeting the $\alpha_4\beta_7$ integrin [102]. Introduction of vedolizumab as a treatment option for patients with UC was a major advance in the field, given that vedolizumab modulates gut-specific inflammation [103].

Vedolizumab has demonstrated efficacy and safety for the induction and maintenance of remission of patients with moderate-to-severe UC (Table 5) [104–107]. Vedolizumab had greater efficacy in patients with UC than in those with CD in a long-term study (18 months) [104]. Overall, clinical remission (partial Mayo score ≤2 with no individual subscore >1) and response (decrease from baseline ≥2 and ≥25% in partial Mayo score, and decrease of ≥1 point in rectal bleeding subscale score or rectal bleeding subscale score ≤1) were achieved by 88% and 49%, respectively, of patients with UC by Day 491; 40% and 70% of patients with CD achieved clinical remission

Table 5. Clinical trials of vedolizumab in patients with moderate-to-severe UC.

Study and treatment(s)	Patient population and definition of severity	Efficacy outcomes
GEMINI 1 [106] *Induction phase*: Vedolizumab 300 mg IV vs. PBO on D 1 and 15 *Maintenance phase*: Vedolizumab 300 mg every 8 wk, vedolizumab every 4 wk, or PBO for up to 52 wk	Moderate-to-severe UC (extending ≥15 cm from anal verge) • Mayo score ≥6 and ≤12, with endoscopic subscale score ≥2	*Induction phase*: Response[a] at Wk 6: vedolizumab vs. PBO, 47.1% vs. 25.5% ($p < 0.001$) *Maintenance phase*: Remission[b] at Wk 52: vedolizumab every 8 wk, vedolizumab every 4 wk, vs. PBO, 41.8, 44.8%, vs. 15.9% ($p < 0.001$ for both vs. PBO)
GEMINI LTS [105] OL tx with vedolizumab 300 mg every 4 wk[c]	Moderate-to-severe UC (extending ≥15 cm from anal verge) [106] • Mayo score ≥6 and ≤12, with endoscopic subscale score ≥2	Remission[d] at Wk 28: 25%; and at Wk 52: 25% Response[e] at Wk 28: 53.1%; and at Wk 52: 37.5%
Parikh, et al. [104] OL tx with vedolizumab 2, 6, or 10 mg/kg loading dose administered on D 1, 15, and 43; maintenance dosing every 8 wk for 18 mo	Active UC extending proximal to the rectum (confirmed by endoscopy and/or histopathology) • PMS ≥2 and ≤7	Remission[d] on D 43: 59% • 37% of pts with PMS ≥4 at baseline achieved remission on D 43 Response[e] on D 43: 31% • 58% of pts with PMS ≥4 at baseline achieved response on D 43
Amiot et al. [107] Vedolizumab 300 mg IV at Wk 0, 2, and 6, and then every 8 wk, for up to 52 wk	Moderate-to-severe UC Mayo score ≥6	Clinical remission[f] at Wk 14: 39% Corticosteroid-free clinical remission[f] at Wk 14: 36% Clinical response[g] at Wk 14: 57% Corticosteroid-free clinical response[g] at Wk 14: 50%

[a]Response defined as a decrease from baseline in Mayo score ≥30% and ≥3, with either a rectal bleeding subscale score ≤1, or a decrease from baseline in rectal bleeding subscale score ≥1.
[b]Remission defined as Mayo score ≤2, with no individual subscale score >1, and endoscopic subscale score ≤1 (mucosal healing).
[c]Responders to vedolizumab at Wk 6 in GEMINI 1 study, but who discontinued study due to lack of response with every 8 wk dosing.
[d]Remission defined as a PMS ≤2, with no individual subscale score >1.
[e]Response defined as a decrease from baseline in PMS ≥2 and ≥25%, with either a decrease from baseline in rectal bleeding subscale score ≥1 or a rectal bleeding subscale score ≤1.
[f]Remission defined as PMS <3 with combined subscores for stool frequency and rectal bleeding ≤1.
[g]Response defined as decrease from baseline in PMS ≥3 and ≥30%, with either a decrease from baseline in rectal bleeding subscale score ≥1 or an absolute rectal bleeding subscale score ≤1.
D: day(s); GEMINI 1: study of vedolizumab in patients with moderate to severe UC; GEMINI LTS: OL study of vedolizumab in patients with UC and Crohn's disease; IV: intravenous; LTS: long-term extension study; mo: month(s); OL: open-label; PBO: placebo; PMS: partial Mayo score; pts: patients; tx: treatment; UC: ulcerative colitis; wk: week(s).

(Crohn's Disease Activity Index (CDAI) score ≤150) or response (decrease from baseline ≥70 in CDAI score), respectively, by Day 491. In this study, 19 patients with UC or CD were receiving corticosteroids at baseline; 79% of these patients either discontinued corticosteroids during the study or decreased corticosteroid dosing by >50%. In the GEMINI 1 study of patients with moderate-to-severe UC (Mayo score 6–12), a significantly greater percentage of patients receiving vedolizumab on Days 1 and 15 achieved clinical remission (Mayo score ≤2, with no subcale score >1) or response (decrease from baseline ≥3 and ≥30% in baseline Mayo score, with decrease in rectal bleeding subscale score of ≥1 point or rectal bleeding subscale score ≤1), compared with placebo at Week 6 (remission: 16.9% vs. 5.4%, respectively; $p = 0.001$; response: 47.1% vs. 25.5%, respectively; $p < 0.001$) [106]. Further, mucosal healing (Mayo endoscopic subscale score ≤1) was achieved by 40.9% and 24.8% of patients receiving vedolizumab or placebo, respectively, at Week 6 ($p = 0.001$). Patients with a response to vedolizumab in the induction phase could continue to receive vedolizumab once every 4 or 8 weeks, or placebo, in the maintenance phase of the GEMINI 1 study. At Week 52, clinical remission was achieved by 44.8% of patients receiving vedolizumab every 4 weeks, 41.8% of patients receiving vedolizumab every 8 weeks, and 15.9% of patients receiving placebo ($p < 0.001$ for either vedolizumab group vs. placebo). Mucosal healing at Week 52 was also achieved by a significantly greater percentage of patients receiving vedolizumab every 4 weeks (56%) or every 8 weeks (51.6%), compared with placebo (19.8%; $p < 0.001$ for both groups vs. placebo). Corticosteroid-free remission favored more frequent dosing of vedolizumab: 45.2% and 31.4% of patients receiving treatment every 4 and 8 weeks, respectively, achieved this outcome at Week 52, compared with 13.9% of patients receiving placebo. The presence of antibodies against vedolizumab was detected in 3.7% of patients during the course of the study; only 1% of patients had ≥2 consecutive samples that were positive through Week 52. Thus, data from the GEMINI 1 study further demonstrated the efficacy (i.e. improvement of both clinical symptoms and mucosal healing) of vedolizumab for the induction and maintenance of moderate-to-severe UC. A recent integrated safety analysis of six clinical studies showed that long-term treatment (i.e. up to 5 years) with vedolizumab was well tolerated in patients with moderate to severe UC [108]. The number of patients experiencing an adverse event (AE) or serious AE (SAE) was less per 100 person-years with vedolizumab versus placebo (AE, 198.4 vs. 351.6, respectively; SAE, 13.7 vs. 22.6).

3.7. Hospitalized patients with UC

All therapies approved for UC, irrespective of disease severity, are based on clinical trials conducted in the outpatient setting. The American College of Gastroenterology 2010 guidelines recommend that patients with severe UC requiring hospitalization due to toxicity receive IV corticosteroids [22]. Prior to more widespread use of TNF-α antagonists in the setting of the hospitalized patient with UC, IV cyclosporine was administered as an alternative to

colectomy based on convincing results of a publication by Lichtiger et al. in 1994 [109]. Briefly, a significantly greater percentage of patients with severe UC receiving IV cyclosporine achieved improvement in the clinical activity score (i.e. response) within 7 days (mean; range, 3–14 days) compared with placebo (82% vs. 0%, respectively; $p < 0.001$). Further, 100% of patients who initially received placebo and then received IV cyclosporine had a therapeutic response. Subsequent studies showed that cyclosporine as a bridge to immunomodulators reduced the 5-year risk of colectomy by approximately 50% [110,111]. A retrospective study of IV cyclosporine at different doses (i.e. 2 mg/kg/d or 4 mg/kg/d) showed similar results over time, with 62.7% of patients remaining colectomy-free after more than 2 years of follow-up [112]. Short-term (i.e. within 2 weeks) colectomy rates did not differ between IV cyclosporine 2 mg/kg/d or 4 mg/kg/d (8.6% vs. 13.1%, respectively) [113]. However, the use of cyclosporine has been limited to higher volume referral centers due to a number of safety concerns, including the risk of opportunistic infections (e.g. *Pneumocystis carinii* pneumonia (PCP)) and a reported 3.5% mortality rate [110–112,114].

Results from small, often uncontrolled studies, are emerging on the role of TNF-α antagonist therapy in the hospitalized patient and, despite conflicting results, there is increased use of infliximab in this setting [115–119]. Infliximab was initially perceived to be easier to use than cyclosporine with lack of daily drug monitoring and, possibly, safer given the absence of PCP prophylaxis [119]. The results of the Study Comparing Cyclosporine With Infliximab in Steroid-Refractory Severe Attacks of Ulcerative Colitis (CYSIF) study showed that a comparable percentage of patients receiving 1 dose of infliximab 5 mg/kg or daily IV cyclosporine 2 mg/kg achieved a clinical response at Day 7 (84% vs. 86%, respectively; $p = 0.8$) and failed treatment (i.e. lack of clinical response) at Day 98 (54% vs. 60%; $p = 0.5$) [120]. Further, long-term maintenance data (i.e. median 5 years) from the CYSIF study showed that patients receiving infliximab or cyclosporin had similar colectomy-free survival (65% vs. 61%, respectively).

However, real-world experience did not always mirror the success of infliximab as reported by the CYSIF study. Emerging data on the impact of inflammation on the pharmacokinetics of infliximab may, in part, explain variations in efficacy. Low serum infliximab concentrations are commonly observed in patients with UC with low concentrations of albumin and high concentrations of C-reactive protein (CRP), both surrogate markers for disease severity [121,122]. An interesting study conducted at the University of Amsterdam hospital demonstrated that patients lacking response to infliximab had higher fecal concentrations of infliximab compared with responders at Week 2 and Month 3, suggesting colonic loss of infliximab [123]. Moreover, colonic tissue had higher anti-TNF concentrations in the face of higher inflammatory burden, suggesting that higher doses of drug may be needed in patients with more severe disease activity [124]. A retrospective study examining accelerated induction dosing (i.e. three infusions within 24 days), compared with the standard 42 days did show a reduction in early colectomy rates (i.e. 8 weeks; $p = 0.04$); however, no such difference was seen when extended out to 2 years [125]. Drug-concentration-based dosing, however, was not used to drive dosing, which could explain the lack of long-term benefit. *Post hoc* analysis of the ACT 1 and ACT 2 studies demonstrated that patients with higher serum infliximab concentrations had higher steroid-free remission rates compared with patients with lower serum infliximab concentrations at Weeks 30 (ACT 1 and ACT 2) and 54 (ACT 1 only) [126]. As we gain a better understanding of what variables impact infliximab clearance, infliximab 10 mg/kg induction dosing has been proposed as an alternative to infliximab 5 mg/kg in patients with risk factors for rapid clearance. Studies are needed to show the superiority of 10 mg/kg dosing to standard or accelerated 5 mg/kg dosing in the induction of hospitalized UC patients.

3.8. Indications for surgery

Indications for surgery in patients with UC include life-threatening events, such as hemorrhage and toxic megacolon, or evidence of or risk for carcinoma [22,127]. However, for most patients, surgery becomes an option when their UC becomes refractory to treatment [22,127,128]. Surgery is often viewed by patients and physicians as a last resort, but there are multiple studies that report improved quality of life in patients who have undergone ileal pouch anal anastomosis (IPAA) [129–131].

Postoperative complications with IPAA include pouchitis, fistula, strictures, and frequent loose stools requiring antidiarrheal therapy. These complications must be discussed with patients so they are prepared to manage any postoperative issues that arise in a timely manner [127,128,132,133]. Additionally, it is well documented that pelvic surgeries like IPAA and creation of a J pouch can impact female fertility [134,135]. In a large cohort study of women of child-bearing age, the fertility rate was lower in women with UC who received surgical treatment for the condition compared with the general female population [136]. In addition, it is estimated that the infertility rate is approximately three times higher in women who have undergone IPAA compared with women with UC who have not received surgical treatment, due to adhesions that can form around the fallopian tubes and ovaries of women in the former population [137,138].

It should be noted that all of the studies of surgical treatment for UC that have been mentioned in this review are retrospective or based on analysis of large databases. Prospective studies in the era of laparoscopic techniques are needed to truly quantify the impact of IPAA on fertility in women with UC.

3.9. Tight control and treat-to-target paradigm

Both physicians and regulatory agencies are moving toward mucosal healing as the target of choice to define therapeutic success. The selecting therapeutic targets in inflammatory bowel disease (STRIDE) working group proposed that normalization of bowel habits and absence of rectal bleeding, in addition to evidence of mucosal healing, should be the target of therapies for UC [139]. They also suggested clinicians evaluate patients every 3 months after initiating therapy until stable. Further, patients with symptoms of UC should undergo endoscopic evaluation at least every 3–6 months after initiating therapy (Figure 1) [139], to determine if treatment has achieved mucosal

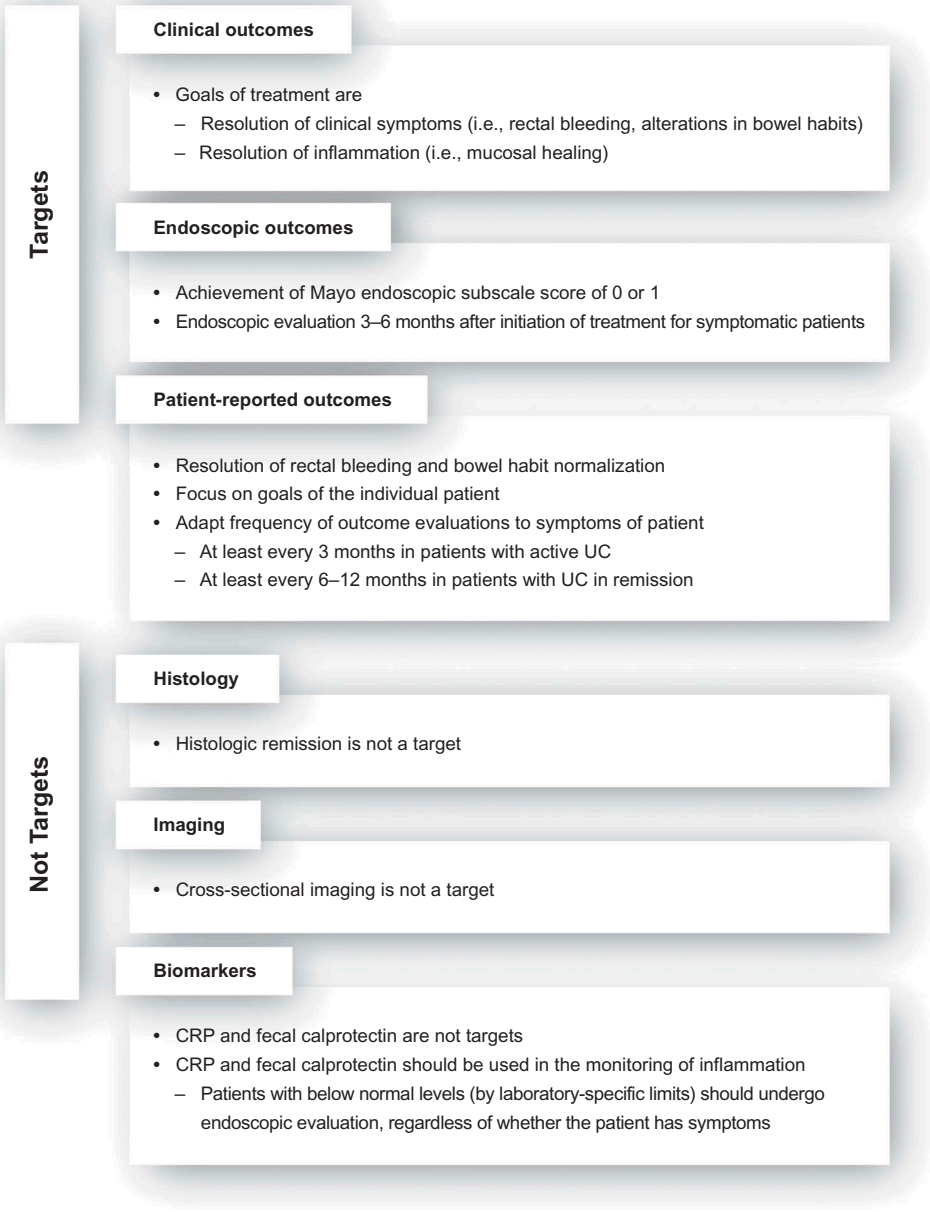

Figure 1. Treat-to-target recommendations for UC from the International Organization for the Study of Inflammatory Bowel Diseases.
CRP: C-reactive protein, UC: ulcerative colitis
Data from Peyrin-Biroulet, et al. *Am J Gastroenterol*. 2015;110:1329 [139].

healing (i.e. Mayo endoscopic subscale score ≤1). Bouguen et al. demonstrated that a greater percentage of patients who underwent routine endoscopic evaluation 6 months after starting any inflammatory bowel disease (IBD) therapy, and received subsequent therapeutic escalation in the face of persistent mucosal inflammation, achieved mucosal healing over time compared with patients who received no adjustments in treatment ($p < 0.0001$) [140]. There is still work to be done to be able to implement a treat-to-target philosophy that both patients and physicians can wrap their arms around, as it is often hard to convince patients who feel well clinically to escalate therapy based on endoscopic evidence of disease. This would also mean a cultural change for most clinicians managing patients with IBD. The treat-to-target objectives for RA denote that disease activity should be assessed every 3 months and treatment adjusted accordingly [141]. Disease activity assessment is more complex in IBD than RA; thus, it has proven more difficult to implement tight control paradigms in IBD. However, noninvasive serum and fecal biomarkers may be useful surrogate markers for mucosal integrity in patients with UC. The STRIDE group does suggest that a fecal calprotectin test may be helpful to direct which patients may merit an endoscopic evaluation but does not substitute for endoscopy [139]. That being said, if fecal calprotectin is benchmarked against endoscopy, fecal calprotectin can then be used to monitor disease activity and to evaluate therapeutic responsiveness. Fecal calprotectin was shown to be predictive of relapse for up to 4 months before clinical symptoms were reported, albeit in CD [142,143]. CRP may not be as useful in

UC as it is in CD as a biomarker of active inflammation [139]. The push for mucosal healing comes from data that support ongoing disease activity, which is associated with increased dysplasia and colon cancer risk, as well as higher risk of colectomy [28,144].

3.10. Where does the moderate patient fall?

The therapies reviewed herein have been grouped based on their indication for either mild-to-moderate disease activity or moderate-to-severe disease activity. This nomenclature does render defining and managing the true 'moderate' patient more difficult. Both patients and physicians often feel comfortable with 5-ASA therapy for the management of mild disease activity and, conversely, a biologic-based therapy for severe disease activity. The question remains as to whether patients with moderate disease should be defined as those who fail to achieve mucosal healing while receiving 5-ASA therapy, in the absence or presence of persistent rectal bleeding. It should be noted that a Mayo score between 6 and 9 is not typically measured outside a clinical trial setting, so more clinically applicable definitions should be described. If indeed 5-ASA failure is the correct definition, then the next question may be 'what is the best maintenance treatment for this subset of patients?' *Post hoc* analyses from the TNF-α antagonist and anti-integrin antibody trials suggest that patients with moderate disease activity respond better than those with more severe disease [106,145]. For patients with moderate UC, patient preference and economic costs may factor into the decision to use infliximab, adalimumab, or golimumab, while vedolizumab may be used in patients with or without prior exposure to TNF-α antagonists [146]. More research needs to be conducted in this group of patients to determine if traditional immunomodulators, such as thiopurines, are inferior to biologics as it relates to mucosal healing and subsequent long-term outcomes before treatment algorithms will be changed for the patient with moderate symptoms.

4. Conclusion

The armamentarium of therapeutic agents available for the management of patients with UC has grown in recent years. Positioning of therapies is dependent on disease extent (e.g. distal UC, extensive UC) and disease severity (i.e. mild, moderate, severe). In addition to the overall efficacy and safety profiles of agents available for the induction and maintenance of remission of UC, other outcomes examined in clinical trials (e.g. corticosteriod-free remission, mucosal healing) that may affect the disease course in patients should be considered in the management of patients with UC. Our current guidelines should be updated to take disease severity, novel approved therapeutic targets, and proposed sequence of targets into account. For example, the literature supports the use of infliximab in hospitalized UC patients or outpatients with severely active, steroid-refractory disease, but a recent publication demonstrated that primary nonresponders to infliximab had a high colectomy rate, and that switching within class did not result in a significant change in outcomes [147]. Moreover, these patients also had increased rates of primary nonresponse when switching within class compared with swapping out of class, for example, to vedolizumab [147]. Clinicians and updated guidelines must consider time to onset of action, patient response to steroids (refractory vs. responsive), and disease severity when choosing therapies for patients with UC. As new biologic and small-molecule drug targets become available, choosing the right therapy for the right patient with UC at the right time will be instrumental in changing the natural history of disease and improving the quality of life of patients with UC.

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Declaration of interest

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