REVIEW

Systematic Literature Review of Real-World Evidence on Dose Escalation and Treatment Switching in Ulcerative Colitis

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Background: Currently approved biologic therapies for moderate-to-severe ulcerative colitis have well-established efficacy. However, many patients fail to respond or lose response, leading to dose escalation or treatment switching.

Objective: We sought to identify real-world evidence on dose escalation and treatment switching and associated clinical and economic outcomes among adults with ulcerative colitis treated with infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, or tofacitinib.

Methods: We conducted a systematic search of Embase, MEDLINE (up to 26 August 2020), and conference proceedings (2017−2020) for studies in adults with ulcerative colitis to assess clinical response and remission, colectomy, adverse events, and economic outcomes related to dose escalation and treatment switching.

Results: In 56 studies, dose escalation and treatment switching involving infliximab and/or adalimumab were most frequently investigated. Rates of clinical response after dose escalation were 20–95% (1.8–36 months), clinical remission rates were 10–94% (1.8–36 months), colectomy rates were 0–33% (12–38 months), and adverse event rates were 0–18%. Treatment switching rates in 21 studies were 4–70% over 3–62 months, with switch due to loss of response rates of 4–35% over 12–62 months (7 studies). Up to 35% of patients underwent colectomy 12−120 weeks after switching, and 13–38% experienced adverse events. Data relating to economic outcomes were limited to tumor necrosis factor inhibitors, but demonstrated increased direct costs associated with both dose escalation and treatment switching.

Conclusion: Dose escalation and treatment switching are common with existing therapies. However, clinical response and remission rates vary, and a proportion of patients fail to achieve optimal clinical and economic outcomes. This highlights the need for more efficacious and durable treatments for patients with moderate-to-severe ulcerative colitis.

Keywords: ulcerative colitis, real-world evidence, systematic literature review, biologic therapies, tofacitinib

Plain Language Summary

Although biologic therapies are effective treatments for patients with moderate-to-severe ulcerative colitis, many fail to respond or lose response over time. These patients may then receive higher doses or more frequent doses of their therapy (called dose escalation) or may switch treatments. We performed a systematic literature review to gather real-world evidence of clinical and economic outcomes for patients who experience dose escalation or treatment switching, including rates of clinical response (improvement in disease activity), clinical remission (little or no disease activity visible endoscopically), colectomy (a surgical procedure to remove all or part of colon), and adverse events, as well as direct healthcare costs. The treatments included in the search were the biologic therapies infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab and the small molecule tofacitinib. We found 56 studies reporting outcomes and treatment patterns for these treatments, with the most data for infliximab and adalimumab. Clinical outcomes varied widely, with rates of clinical response after dose escalation of 20–95%, clinical remission rates of 10–94%, colectomy rates up to 33%, and adverse event rates up to 18%. Between 4% and 35% of patients switched treatments; of these, up to 35% underwent colectomy and 13–38% experienced adverse events. Direct costs were higher after both dose escalation and treatment switching. Since clinical

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outcomes were so varied and costs were higher for patients experiencing these treatment strategies, the study suggests a need for more effective and durable treatments for patients with moderate-to-severe ulcerative colitis.

Introduction

Ulcerative colitis (UC) is a chronic, relapsing-remitting disease characterized by inflammation of the rectal and colonic mucosa.[1] UC is a major form of inflammatory bowel disease (IBD),[2] and its worldwide incidence and prevalence are rising.[3] The Montreal classification categorizes UC into 3 subgroups defined by disease extent: ulcerative proctitis (rectal involvement only), left-sided or distal UC (inflammation limited to a proportion of the colorectum distal to the splenic flexure), and extensive colitis or pancolitis (involvement extending proximal to the splenic flexure).[4] The clinical course of UC is characterized by periods of remission and exacerbation that often require the escalation of doses, switching of treatments, or, ultimately, surgery.[5]

The updated Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) consensus identifies clinical response as an immediate UC treatment target, clinical remission as an intermediate treatment target, and endoscopic healing as a long-term target; moreover, the statement notes that clinical response and remission are more valuable as therapeutic goals in UC than in Crohn's disease.[6] Improvement in signs and symptoms of UC, histologic healing, and reduction in the risk of adverse long-term outcomes such as colonic dysplasia and colectomy are also reported to be treatment goals of interest.[6–9] First-line treatment for mild or moderate UC includes aminosalicylates (5-ASAs), such as sulfasalazine or mesalazine, which are recommended to reduce inflammation.[10] 5-ASAs are effective for many patients; however, other patients fail to achieve remission on this therapy and may, therefore, require treatment with corticosteroids and, when remission is still not achieved, biologic therapies.[11] Moderate-to-severe UC is commonly managed with biologic agents, such as the tumor necrosis factor inhibitor (anti-TNF) therapies infliximab (IFX), adalimumab (ADA), and golimumab (GOL), as well as the integrin $\alpha 4\beta 7$ inhibitor vedolizumab (VDZ) and the interleukin (IL)-12 and IL-23 inhibitor ustekinumab (UST).[10,12,13] Pharmacologic therapy options also include an established small molecule, the Janus kinase (JAK) inhibitor tofacitinib (TOF), and newer small molecules, such as the JAK inhibitors upadacitinib and filgotinib, and ozanimod, a sphingosine 1-phosphate receptor modulator. Clinical guidelines on the management of UC recommend treatment with biologic agents or TOF for patients with steroid-dependent active disease, oral steroid-refractory active disease, moderate-to-severe disease, and moderate disease that is refractory to thiopurines.[10,12,14]

The use of biologics in the treatment of UC has led to improved outcomes, including higher rates of clinical remission and fewer surgeries.[15,16] Nonetheless, about one-third of inflammatory bowel disease patients fail to respond to treatment with biologics (primary nonresponse) and 23–46% of patients experience loss of response (LOR) over time (secondary LOR).[17–19] In such instances, physicians may consider escalating the dose of the biologic or switching to an alternative treatment.[17,18] These approaches have become important tools in the management of UC.[20] However, dose escalation and treatment switching may have clinical and safety implications and potential economic consequences. The objective of the study was to identify real-world evidence on dose escalation and treatment switching and associated clinical and economic outcomes among adults with ulcerative colitis treated with IFX, ADA, GOL, VDZ, UST, or TOF.

Materials and Methods
Data Sources and Search Strategies

A systematic literature review (SLR) was conducted to identify studies published in Embase and MEDLINE (via www.embase.com) from database inception up to 26 August 2020. In addition, conference proceedings from meetings of the European Crohn's and Colitis Organisation, the American College of Gastroenterology, United European Gastroenterology Week, and Digestive Disease Week held from 2017 to 2020 were searched to identify abstracts reporting recent not fully published studies.

Search terms for the SLR were developed in accordance with the PICOS framework (which defines study population, interventions/comparators, outcomes, and study type; see Supplementary Table 1 for the full PICOS statement) and included details on specific aspects of the study question, which was to identify real-world evidence on clinical, safety, and economic outcomes associated with dose escalation and treatment switching with anti-TNF agents, VDZ, UST, and TOF. The exact search terms (including EMTREE terms and free-text search terms) are presented in Supplementary Table 2.

Study Selection

Study eligibility criteria were expressed in terms of the PICOS framework. The population of interest comprised adult UC patients (aged ≥18 years) who were naive to anti-TNF therapy and those who had received prior anti-TNF therapy. Therapies of interest were IFX, ADA, GOL, VDZ, UST, and TOF. Studies considered relevant were those that reported outcomes of interest (Supplementary Table 1) associated with dose escalation and treatment switching for the target therapies.

To assess the eligibility of studies, 2 reviewers independently examined titles and abstracts identified using the search strategy according to the prespecified inclusion/exclusion criteria. The full text of articles that were identified as potentially relevant based on title and abstract were then critically reviewed by 2 reviewers screening independently. At each step, disagreements about any articles were referred to a third reviewer for a consensus. From the eligible studies, the following data were extracted: study design, baseline patient characteristics, and clinical, safety, and economic outcomes related to dose escalation and treatment switching. Clinical outcomes extracted included clinical response, clinical remission, steroid-free clinical remission, avoidance of colectomy, and safety.

Definition of Terms

Dose escalation or optimization of UC therapies can be achieved by increasing the dose or shortening the interval between doses (ie, dose remains at the approved level but is administered more frequently). Table 1 presents information from the United States FDA-approved Prescribing Information and the European Union EMA-approved Summary of Product Characteristics on the treatments of interest in this review and their regular dosages, which can be escalated or given in a shortened dosing interval in adults with UC.

Results

Figure 1 (PRISMA flow diagram) summarizes the identification and selection of 56 included studies (52 full-text articles, 4 conference abstracts). Of the 56 articles and abstracts, 26 reported on dose escalation only, 7 reported on treatment switching only, 22 reported on both dose escalation and treatment switching, and 1 reported on interval lengthening. Characteristics of the included studies are summarized in Supplementary Table 3.[21–76]

The following outcomes of interest related to dose escalation were reported for 17 studies (some reported in more than 1 study): clinical response, n=11; clinical remission, n = 11; colectomy, n = 8; adverse events (AEs), n = 6; and economic outcomes, n = 2. The following outcomes related to treatment switching were reported in 12 studies (some reported in more than 1 study): clinical response, n = 6; clinical remission, n = 9; corticosteroid-free remission, n = 5; colectomy, n = 8; AEs, n = 6; and economic outcomes, n = 1. Overall, the majority of the studies were retrospective; the predominance of evidence on dose escalation was reported from 2014 to present, while the evidence of treatment switching was reported more consistently over time (Supplementary Figure 1).

Dose Escalation

Of the 48 studies reporting dose escalation, 20 reported dose increases only, 14 reported interval shortening, and 14 reported dose escalation via both methods (Supplementary Table 4).[21–29,31,32,34–38,40–42,45–52,54,55,57–69,71,72,74–76] One study did not describe the method of dose optimization.[24] Follow-up times varied from ≤12 months in 11 studies to >12-≤24 months in 10 studies and >24 months in 8 studies; follow-up times were not reported for the remaining 19 studies. There were 9 reports of dose escalation done to address LOR,[31,44,46,63,66–68,75,76] whereas the remaining 39 dose escalations were done for any reason (Figure 2).[22–29,32,34,35,37,38,40–42,45,47–52,55,57–62,64,65,69,71,72,74] The average rate of escalation by dose increase varied greatly, ranging from 80% to 340% relative to the starting dose (Supplementary Table 5).[26,29,31,35,36,38,40,46,49,52,57,59,61–63,65–69,75] In studies with follow-up times of ≤12 months, the rate of dose escalation was 11.5–44%, whereas in studies with follow-up times of >12-≤24 months and >24 months, the rate of dose escalation was 8.4–73.5% and 4.9–54.0%, respectively (Supplementary Table 4). The highest mean dose increases reported for IFX were 5–22 mg/kg over 8 weeks (340%),[35] 100–370 mg/kg over 4 weeks for GOL (270%),[35] and 40–112 mg biweekly for ADA (180%).[35] Dose escalation by interval shortening alone was reported in 31 studies (Supplementary Table 6);[21–23,26–28,31,32,34,36–38,41,44,46,47,49–52,55,58,59,64–68,70,71,74,75] this most commonly occurred with IFX (from 5 mg/kg every 8 to 4 weeks) and ADA (from 40 mg every 2 weeks to once weekly).

Table 1 Regular Dosages for Drugs Administered in Patients with UC

Drug, Brand (Generic)	Class	Manufacturer	Mode of Administration	EU Dosage in UC	US Dosage in UC
Remicade (infliximab)	Anti-TNF therapy	Janssen Biotech	IV	5 mg/kg at 0, 2, and 6 weeks and every 8 weeks thereafter for the treatment of adult patients	5 mg/kg at 0, 2, and 6 weeks and every 8 weeks thereafter
Humira (adalimumab)		AbbVie	SC	160 mg at week 0 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days) and 80 mg at week 2 (given as two 40 mg injections in 1 day) After induction treatment, the recommended dose is 40 mg every other week via SC injection	160 mg on day 1 (given in 1 day or split over 2 consecutive days), 80 mg on day 15 and 40 mg every other week starting on day 29. Discontinue in patients without evidence of clinical remission by 8 weeks (day 57)
Simponi (golimumab)		Janssen Biotech	SC	Patients with body weight <80 kg → initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter Patients with body weight ≥ 80 kg → initial dose of 200 mg, followed by 100 mg at week 2 and 100 mg every 4 weeks thereafter	200 mg initially administered by SC injection at week 0, followed by 100 mg at week 2 and 100 mg every 4 weeks thereafter
Entyvio (vedolizumab)	Integrin receptor antagonist	Takeda	IV	300 mg administered by IV infusion at 0, 2, and 6 weeks and every 8 weeks thereafter EU SmPC states that some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to IV vedolizumab 300 mg every 4 weeks	IV 300 mg infused over approximately 30 minutes at 0, 2, and 6 weeks and every 8 weeks thereafter
Xeljanz (tofacitinib)	JAK inhibitor	Pfizer	Oral	Induction: • The recommended dose for induction treatment is 10 mg given orally twice daily for 8 weeks • For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance Maintenance: • The recommended dose for maintenance treatment is tofacitinib 5 mg orally given twice daily • For patients with UC who are not at increased risk for venous thromboembolism, tofacitinib 10 mg orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5 mg twice daily and failed to respond to alternative treatment options for UC such as anti-TNF therapy	Induction: • Tofacitinib 10 mg twice daily or extended-release tofacitinib 22 mg once daily for 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response • If needed, continue tofacitinib 10 mg twice daily or extended-release tofacitinib 22 mg once daily for a maximum of 16 weeks • Discontinue tofacitinib 10 mg twice daily or extended-release tofacitinib 22 mg once daily after 16 weeks if adequate therapeutic response is not achieved Maintenance: • Tofacitinib 5 mg twice daily or extended-release tofacitinib 11 mg once daily • For patients with loss of response during maintenance treatment, tofacitinib 10 mg twice daily or extended-release tofacitinib 22 mg once daily may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient
Stelara (ustekinumab)	IL-12/ IL-23 antagonist	Janssen Biotech	IV and SC	A single IV, weight based: • ≤55 kg: 260 mg (2 vials) • 56–85 kg: 390 mg (3 vials) • >85 kg: 520 mg (4 vials) The first SC dose should be given at week 8 following the IV dose. After this, dosing every 12 weeks is recommended	A single IV, weight based: • ≤55 kg: 260 mg (2 vials) • 56–85 kg: 390 mg (3 vials) • >85 kg: 520 mg (4 vials) The SC maintenance dose is 90 mg 8 weeks after the first IV dose and every 8 weeks thereafter

Abbreviations: Anti-TNF, tumor necrosis factor inhibitor; IL, interleukin; JAK, Janus kinase; SmPC, summary of product characteristics; UC, ulcerative colitis.
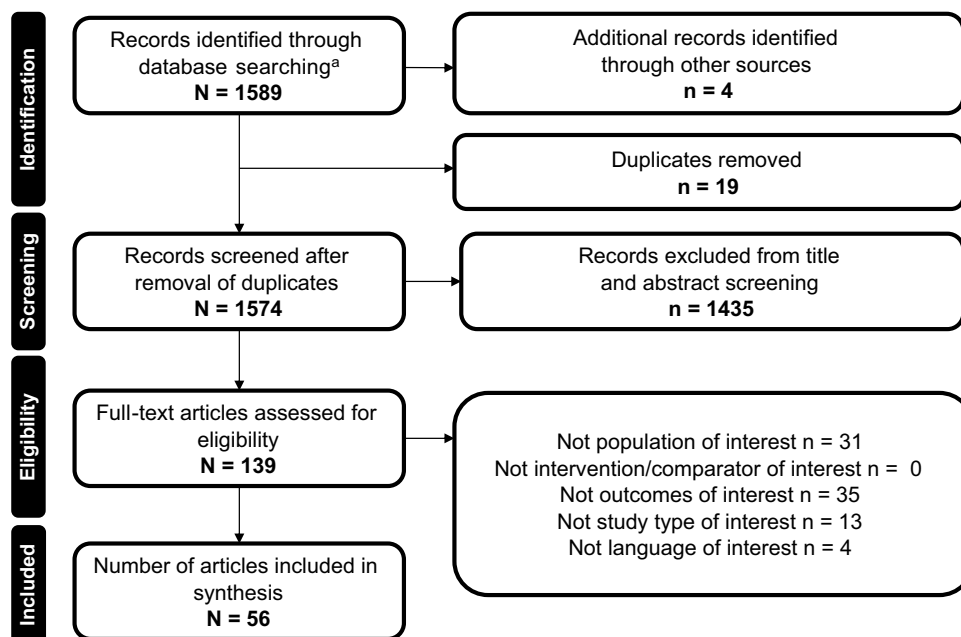
Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for publication screening and selection. [a]EMBASE + Medline.
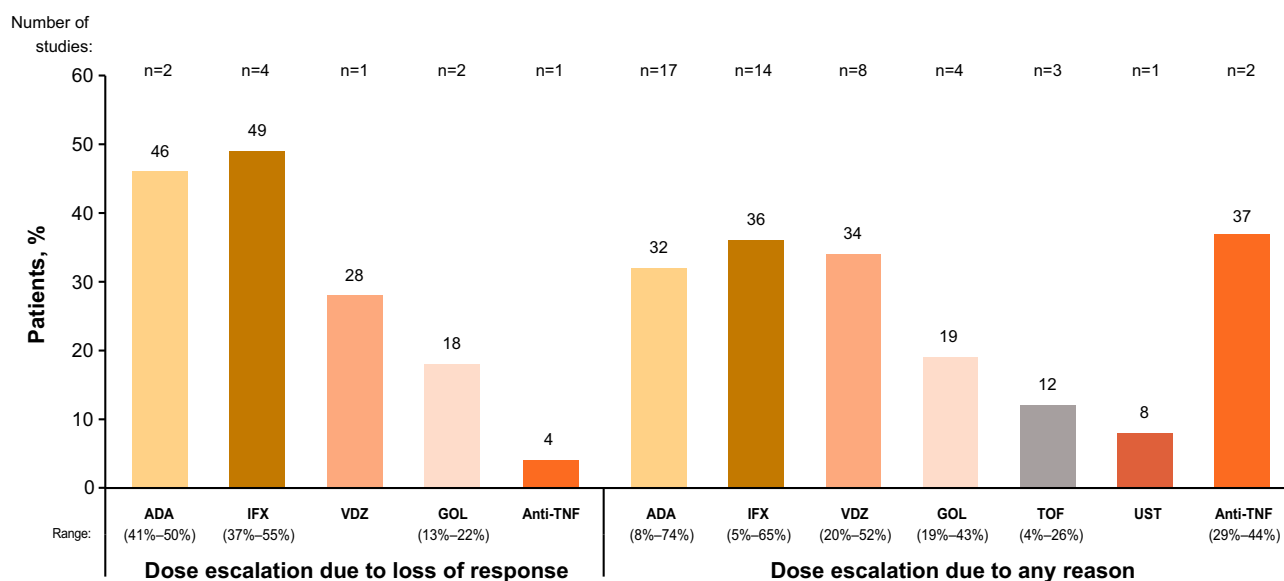

Figure 2 Proportion of patients treated with dose escalation due to loss of response[31,44,46,63,66–68,75,76] or any reason.[22–29,32,34,35,37,38,40–42,45,47–52,55,57–62,64,65,69,71,72,74] Studies originating in multiple countries and including multiple anti-TNF therapies were counted more than once, giving a total number of references higher than the 48 publications found. **Abbreviations**: ADA, adalimumab; GOL, golimumab; IFX, infliximab; TOF, tofacitinib; UST, ustekinumab; VDZ, vedolizumab.

The majority of studies (25; 52.0%) were conducted in mixed treatment-naïve and treatment-experienced populations, in which the experienced patients had at least 1 previous biologic treatment failure. Six studies (12.5%) included only treatment-naïve patients, while 5 (10.4%) included only treatment-experienced patients and 12 (25.0%) did not report patients' prior biologic treatment experience.

The most commonly investigated escalations were for doses of IFX and ADA and were done across follow-up times of 12–62 months and 11–32 months, respectively, with doses escalated in 42% and 34% of patients in daily practice (in 18 and 19 studies) (Supplementary Figure 2). TOF and UST had the fewest studies reporting dose escalation. Time to dose escalation ranged from 0.7 to 29 months (Supplementary Table 4) and was mainly reported in studies of IFX (n = 7) and ADA (n = 10), in which the rates of dose escalation were similar.

Clinical Response

Clinical response after dose escalation was reported in 11 studies,[31,32,40,44,55,61,62,66–69] the majority of which (n = 10) comprised populations of both anti-TNF–naïve and anti-TNF−experienced patients ([Supplementary Table 7]).[31,32,40,55,61,62,66–69] The definition of clinical response was consistent across studies as a 3-point decrease in partial Mayo score or as a decrease in partial Mayo score of ≥50% and a final score of ≤2. The rates of short- and long-term (2.8–15 months) clinical response with IFX dose escalation ranged from 58% to 92% ([Figure 3A]). Short-term (1.8 months) clinical response after ADA dose escalation was reported in 1 study and was achieved by 47% of patients.[67]
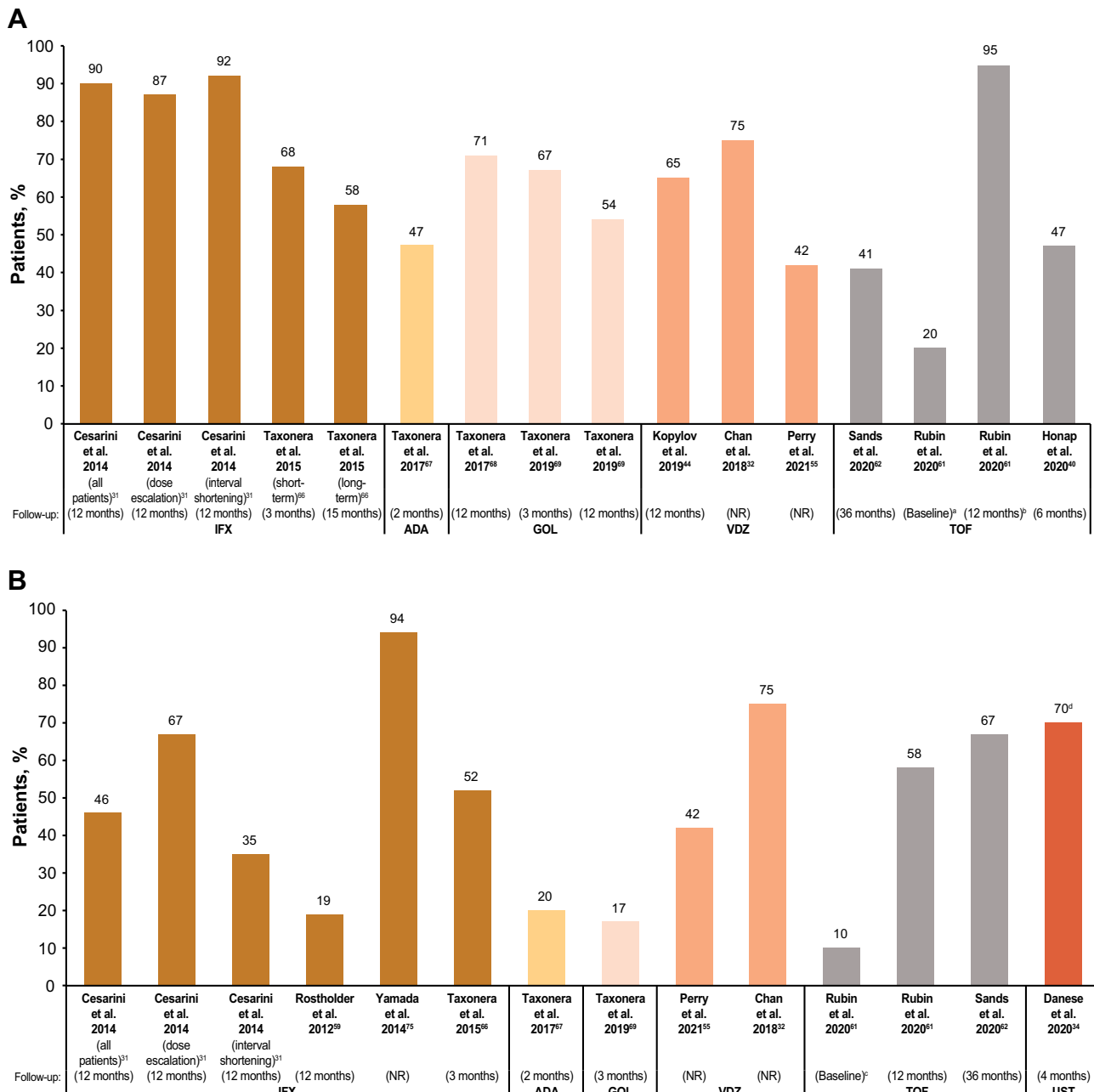
Figure 3 (**A**) Rates of clinical response[31,32,40,44,55,61,62,66–69] and (**B**) clinical remission[31,32,34,55,59,61,62,66,67,69,75] after dose escalation. [a]20% of patients were in clinical remission at time of dose escalation. [b]Partial remission; only 20 observed cases for partial remission at 12 months (ie, data missing for 21 of the original 41 patients). [c]10% of patients were in clinical remission at the time of dose escalation, with such patients who violated protocol being treated with dose escalation at the discretion of the treating physician. [d]Data reported for a subpopulation of patients treated with dose escalation (n=20/40) for whom 16-week follow-up data were available.
Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; NR, not reported; TOF, tofacitinib; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab.

Clinical response after GOL, VDZ, and TOF dose escalations was achieved in 54–71%,[68,69] 42–75%,[32,44,55] and 20–95%[40,61,62] of patients, respectively. No study reported clinical response after UST dose escalation.

Clinical Remission
Clinical remission after dose escalation was reported in 8 studies and 3 abstracts, of which 7 comprised mixed populations of anti-TNF–naïve and anti-TNF–experienced patients (Supplementary Table 8).[31,32,34,55,59,61,62,66,67,69,75] The definition of clinical remission was mostly consistent across studies, defined as a Mayo score of 0–2, although in some studies, the definition was an absence of symptoms or a Modified Truelove and Witts Severity Index score of <4. Clinical remission after IFX dose escalation was reported over 12 months in 4 studies, in which the rate ranged from 19% to 94%[31,59,66,75] (Figure 3B). Short-term (1.8 months) clinical remission after ADA dose escalation was reported in 1 study and was achieved by 19.7% of patients.[67] Clinical remission after GOL, VDZ, TOF, and UST dose escalations was achieved in 16.7%,[69] 41.7–75.0%,[32,55] 9.8–57.6%,[61,62] and 70.0%[34] of patients, respectively.

Colectomy
The need for colectomy for lack of efficacy despite dose escalation was reported in 9 studies (Supplementary Table 9).[31,37,59,64,66–69,75] Five of these studies reported on patients undergoing colectomy after IFX dose escalation, with rates ranging from 0% to 33% across 12–38 months.[31,37,59,66,75] In 1 study, the colectomy rate at 12 months was 20% after IFX dose escalation and 3.8% after IFX interval shortening.[31] Two studies reported rates of colectomy after ADA dose escalation: 10% over 27.6 months in 1 study[64] and 21.0% (16.7% in treatment-naïve patients and 21.9% in treatment-experienced patients) over 17 months in the other study.[67] The colectomy rate after GOL dose escalation was reported in 2 studies: 0.0–2.9% over 12 months.[68,69] No studies reported colectomy outcomes after VDZ, TOF, or UST dose escalation.

Dose De-Escalation
Dose de-escalation data in patients who had initial dose escalation were reported in 8 studies only for ADA and IFX (Supplementary Table 10).[29,31,35,36,50,57,66,67] The overall proportion of patients with dose de-escalation ranged from 17.1% to 80.9%, with mean time to de-escalation of 21 days to 13.6 months.

Adverse Events
Six studies reported AEs associated with dose escalation (Supplementary Figure 3).[31,36,61,62,66,75] Regardless of study duration, IFX dose escalation was associated with variable rates of AEs (0.0–18.0%). Treatment discontinuation due to AEs was reported only after dose escalation of IFX, occurring in 8.9% of patients over 24 months.[66] The rate of AEs associated with TOF dose escalation was 14.0% over 36 months.[62] No safety data were reported for ADA, GOL, VDZ, or UST.

Economic Outcomes
Only 2 studies reported on the costs associated with dose escalation. Black et al (2016) found that ADA dose escalation without subsequent de-escalation was associated with a £1187.00 (8.9%) increase in mean all-cause healthcare costs (defined as any hospital and pharmacy services) over 12 months compared with no escalation; for those patients whose dose was subsequently de-escalated, the increase was £1273.00 (9.5%) (Supplementary Figure 4A).[29] Prescription costs accounted for the majority of UC-related healthcare costs for patients whose dose was escalated and those whose dose was not (97% and 96%, respectively). Pöllinger et al (2019) showed that ADA dose escalation without subsequent de-escalation was associated with a €11,160.00 (44.8%) annual increase in direct drug costs (defined as the mean of all ADA prescriptions); for patients who underwent subsequent de-escalation, there was an increase in annual cost of €7808.00 (31.3%) per year (Supplementary Figure 4B).[57] No studies reported direct or indirect costs associated with IFX, GOL, VDZ, TOF, or UST.

Treatment Switching

Of the 29 studies reporting on treatment switching, 8 reported outcomes for patients with a history of treatment switching (ie, patients had already switched treatments at study outset), with 18–60% of patients switching because of LOR (Supplementary Table 11).[25,33,56,64,68,71,73,74] Of the 8 studies, 7 included only patients who had switched treatments and 4 reported the duration of pre-switch therapy, which ranged from 5.0 to 19.2 months.

The remaining 21 studies reported on treatment switches that occurred during the study observation period, for which follow-up periods ranged from 3 to 62 months (Supplementary Table 12).[22–24,26,30,37–39,41,43–45,47,48,51,53,54,60,63,67,72] In studies with follow-up periods of 3–12 months, rates of switching among all UC patients who initiated biologic treatment ranged from 6% to 50%.[41,44,48,60,63] In studies with follow-up periods of 12–24 months, switching rates ranged from 4% to 70%.[30,38,45,47,67,72] Studies with follow-up periods of >24 months reported switching rates of 4–52%.[22–24,26,37,51,53]

The median time from start of therapy to treatment switch was reported for 2 studies,[48,51] ranging from 3.2 to 7.7 months (Supplementary Table 13). Three other studies reported the time to discontinuation of prior (ie, pre-switch) therapy or time to discontinuation due to LOR.[25,37,74]

The proportion of UC patients who initiated biologic therapy and switched to another biologic specifically because of LOR was reported in 7 studies and ranged from 4% to 35% over follow-up periods of 12–62 months (Supplementary Table 12). No studies reported the median time from LOR to treatment switch.

The most frequently reported switch was from IFX to ADA, reported in 12 studies (Supplementary Figure 5). Six of the studies reported on history of treatment switching, where 100% of patients had switched from IFX to ADA at study outset for any reason.[25,33,56,64,67,71] However, the remaining 6 studies reported on treatment switches that occurred during the study observation period, for which the occurrence of a switch from IFX to ADA ranged from 4% to 53%.[22,26,30,39,43,48] Other common switches were ADA to IFX (n = 8), ADA to GOL (n = 3), and IFX to VDZ (n = 2).

Clinical Response and Remission

Nine studies reported the rates of clinical remission after a treatment switch, and, of these, 6 also reported data on clinical response (Table 2). Notably, the switches reported in 7 of the 9 studies may be considered switching within class (ie, switching between anti-TNF agents), whereas 2 of the studies reported switches between drugs with different mechanisms of action. Studies reported greater proportions of patients achieving clinical remission with increasing time after switch. The proportion of patients who switched treatments and achieved clinical remission ranged from 10% to 73% at follow-up times of <6 months but ranged from 18% to 100% at follow-up times of ≥6 months. Conversely, the proportion of patients reported as showing a clinical response decreased over time. The proportion of patients who switched and achieved clinical remission ranged from 31.6% to 64.7% during follow-up of <6 months (ie, <26 weeks) but ranged from 18.4% to 52.1% during follow-up of >6 months (ie, ≥26 weeks; Table 2). Five studies reported the proportions of patients who achieved corticosteroid-free clinical remission after a treatment switch, ranging from 22% to 79%.[25,33,67,68,71]

Colectomy

The proportion of patients undergoing colectomy after a treatment switch was reported in 8 studies (Supplementary Table 14). Of the 8 studies, 7 were considered studies of switching within class[25,33,64,67,68,71] and 1 reported on switches between drugs with different mechanisms of action.[51,56] Among the studies of switching within class, the rate of colectomy reached 20% over follow-up periods of 12–120 weeks. Among the treatment switching studies, the proportion of patients who underwent colectomy was up to 35% (at 108 weeks).

Adverse Events

Six studies reported AEs associated with treatment switching (Supplementary Figure 6);[25,56,64,71,73,74] 4 of these were studies of switching within class, and the remaining 2 reported AEs after switches between drugs with different mechanisms of action (specifically, IFX and VDZ). Overall, AEs occurred in 13–38% of patients who switched treatment. Four of these studies additionally reported the proportion of patients discontinuing treatment because of AEs after a switch, which ranged from 3% to 20%.

Table 2 Clinical Remission and Clinical Response Following Treatment Switch

Study	Treatment Switch	Patients with UC, n (%)	Patients Who Switched Treatment, n (%)	Time of Assessment	Switched Patients Achieving Clinical Remission, n (%)	Switched Patients Achieving Clinical Response, n (%)
Studies reporting on switching within treatment class[a]						
Baert et al (2014)[25]	IFX>ADA	73 (100)	73 (100)	12 weeks	—	55 (75.3)
Baert et al (2014)[25]	IFX>ADA	73 (100)	73 (100)	12 months (52 weeks)	—	38 (52.1)
Baki et al (2015)[26]	IFX>ADA ADA>IFX	72 (100)	72 (100)	—	2 (2.8)	—
Christensen et al (2015)[33]	IFX>ADA	33 (100)	33 (100)	12 weeks	6 (18.2)	15 (45.5)
Christensen et al (2015)[33]	IFX>ADA	33 (100)	33 (100)	12 months (52 weeks)	6 (18.2)	8 (24.2)
Peyrin-Biroulet et al (2007)[56]	IFX>ADA	10 (100)	10 (100)	—	1 (10)	3 (30)
Taxonera et al (2011)[64]	IFX>ADA	30 (100)	30 (100)	4 weeks	3 (10)	16 (53.3)
Taxonera et al (2011)[64]	IFX>ADA	30 (100)	30 (100)	12 weeks	8 (26.7)	18 (60)
Taxonera et al (2017)[68]	IFX/ADA>GOL	142 (100)	85 (59.9)	8 weeks	45 (52.9)	92 (64.7)
Taxonera et al (2017)[68]	IFX/ADA>GOL	142 (100)	85 (59.9)	12 months	50 (58.8)	—
Tursi et al (2014)[71]	IFX>ADA	15 (100)	15 (100)	24 weeks	11 (73.3)	—
Tursi et al (2014)[71]	IFX>ADA	15 (100)	15 (100)	54 weeks	15 (100)	—
Viola et al (2019)[73]	ADA/GOL>IFX	76 (100)	76 (100)	3 months	29 (38.2)	24 (31.6)
Viola et al (2019)[73]	ADA/GOL>IFX	76 (100)	76 (100)	6 months	29 (38.2)	14 (18.4)
Viola et al (2019)[73]	ADA/GOL>IFX	76 (100)	76 (100)	12 months	26 (34.2)	7 (9.2)
Stefanovic et al (2021)[63]	GOL>IFX	30 (100)	11 (36.7)	13 months (57 weeks)	9 (81.8)	—
Studies reporting on switching treatment MOA[b]						
Stefanovic et al (2021)[63]	GOL>VDZ	30 (100)	3 (10)	13 months (57 weeks)	3 (100)	—
Wang et al (2019)[74]	Anti-TNF>VDZ	5 (12.2)	5 (100)	6 months	5 (100)	—
Wang et al (2019)[74]	Anti-TNF>VDZ	5 (12.2)	5 (100)	12 months	5 (100)	—

Notes: [a]Switching between anti-TNF agents. [b]Switching between drugs with different mechanisms of action.
Abbreviations: Anti-TNF, tumor necrosis factor inhibitor; ADA, adalimumab; GOL, golimumab; IFX, infliximab; MOA, mechanism of action; UC, ulcerative colitis; VDZ, vedolizumab.

Economic Outcomes

One study reported economic outcomes associated with treatment switching. Null et al (2017) found that the mean quarterly total healthcare expenditure was highest for patients who switched from anti-TNFs (n = 399) at US\$15,004 (2014 currency) compared with US\$9632 for the patients who maintained the same treatment at a stable dose (n = 1253), representing a 55.8% cost increase.[48] Most of these costs were accounted for by total anti-TNF–related pharmacy costs (US\$9033 vs US\$7362, respectively) and by total medical costs (US\$5343 vs US\$1723, respectively).

Discussion

This SLR captured real-world evidence on the rates of dose escalation and treatment switching and the associated clinical and economic outcomes among UC patients. Overall, our results showed that dose escalation and treatment switching are commonly required among patients receiving biologic therapies for UC and that rates of clinical response or remission vary considerably. The rates of dose escalation of anti-TNFs, VDZ, TOF, and UST in daily practice ranged from 4.0–65.0%, 20.0–52.1%, 4.3–25.6%, and 8.0%, respectively, and the rates of treatment switching in daily practice ranged from 4.0% to 70.0%.

Findings on the rate of dose escalation were consistent with those reported in a recent SLR on dose escalation and treatment switching in UC by Gemayel et al (2019).[5] However, the rate of treatment switching in daily practice reported in the current SLR was approximately 3-fold greater than that reported by Gemayel et al (range: 1.0% at 6 months to 26.0% at 2 years). This may be explained in part by the emergence of new treatments for UC since the publication of Gemayel et al (data captured 2006–2017) that have increased switching opportunities in daily practice. This SLR also captured a greater number of reasons for switching (LOR, infusion reactions, AEs, patient preferences, and primary nonresponse) compared with Gemayel et al, which reported only LOR and AEs as reasons for treatment switching.[5]

Similarly, time to dose escalation or treatment switching among UC patients, where reported, ranged between 0.7–29 months and 3.2–7.1 months, respectively. Data on time to dose escalation with GOL, VDZ, and TOF were scarce, possibly owing to the lack of studies assessing dose escalation with these agents. These findings were also consistent with those from Gemayel et al.[5] However, the available data from the current study compared with those reported by Gemayel et al demonstrate that time to dose escalation is shorter with GOL (4.7 months) and TOF (1.3 months) than with IFX (up to 29 months), ADA (up to 8.0 months), and VDZ (up to 18.7 months). Further research is needed to understand the factors that influence the time to dose escalation for each drug.

After dose escalation and treatment switching, the proportions of patients achieving clinical response and clinical remission varied greatly. With regard to treatment switching, it is not possible to meaningfully compare the proportions of patients achieving clinical response or remission after switching within a single drug class vs switching between drugs with different mechanisms of action, owing to the small number of studies reporting on switches between drugs with different mechanisms of action.

Considerable proportions of patients were reported to still require colectomy after dose escalation (up to 33% in moderate-to-severe UC patients) or treatment switching (35%). Real-world data on AEs were limited to 6 studies associated with either treatment pattern. AEs were reported to have occurred after dose escalation of IFX and TOF and after switches to ADA, IFX, and VDZ.

A large degree of heterogeneity was observed in the rates of dose escalation and treatment switching across the studies included in this review. Such heterogeneity may stem from the considerable differences noted across the studies in terms of sample size, duration of follow-up, study setting (from single-center to large claims database studies) and region. The noted differences in sample size, follow-up, and study setting may also in part explain the heterogeneity seen in clinical response and remission. Furthermore, most of the evidence was derived from retrospective studies. Hence, it is difficult to draw any conclusion based on any single real-world study by comparing and interpreting the proportion of patients treated with dose escalation or treatment switching across the different therapies and lines of treatments, as well as to make any correlations between the use of prior anti-TNF therapy and the time to dose escalation or treatment switching. However, future meta-analyses of retrospective studies may focus on a quantitative comparison.

Other limitations encountered in this review suggest a need for caution when interpreting the findings. Durations of follow-up were mostly reported as 1–2 years, necessitating longer-term data on the current anti-TNF biologic therapies for UC. There was a lack of data on some clinical outcomes; rates of clinical relapse and hospitalization, the incidence of colorectal cancer, and rates of endoscopic remission after dose escalation and treatment switching could not be compared between treatments.

Data regarding the economic outcomes associated with dose escalation and treatment switching were particularly scarce and limited to direct costs associated with ADA or unspecified anti-TNF therapy; no studies assessed reported indirect costs. However, it should be noted that an analysis of the economic outcomes of dose escalation and treatment switching may be feasible based on the clinical data identified during this SLR. That is, the data regarding levels of dose escalation, types of treatment switch and the clinical outcomes associated with these may be used as the basis for an economic analysis of dose escalation and treatment switching for the drugs included in the scope of this study.

Further research on economic outcomes of real-world UC treatment patterns is warranted by the current or anticipated market entry of biosimilars for IFX and ADA. Biosimilar uptake has been uneven across different regulatory landscapes, which incentivize biosimilar use to varying degrees.[77,78] Biosimilar use is generally expected to increase in the coming years, as real-world evidence accrues to suggest that clinical outcomes are comparable between originator and biosimilar products, at lower economic cost.[77–80] The degree of cost savings with biosimilars compared with originator products varies, but, through competition with originator products, biosimilar use is expected to drive down prices overall.[80,81] With lower acquisition costs, biosimilar dose escalation or treatment switching to a biosimilar would, prima facie, be expected to lower direct costs compared with dose escalation and treatment switching with originators; however, real-world evidence of the economic outcomes associated with these treatment patterns is, as yet, unavailable.

Conclusion

Overall, this SLR demonstrated that dose escalation and treatment switching are commonly required for patients with moderate-to-severe UC in routine clinical practice and are associated with variable clinical response and clinical remission rates. This may be indicative of suboptimal clinical and economic outcomes, underscoring the need for more efficacious and durable treatments for patients with moderate-to-severe UC.

Data Sharing Statement

Bristol Myers Squibb's policy on data sharing can be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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