Real-world effectiveness and safety of advanced therapies for the treatment of moderate-to-severe ulcerative colitis: Evidence from a systematic literature review

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Plain language summary

We conducted a systematic literature review to understand the safety and effectiveness of available therapies in the real world for the treatment of moderate-to-severe ulcerative colitis. We found that vedolizumab and tofacitinib were the most assessed therapies. Remission rates were numerically higher with tofacitinib vs vedolizumab, and for vedolizumab vs anti-tumor necrosis factor-α (TNFα). Tofacitinib was comparable with ustekinumab. Studies have reported that infliximab was the most effective anti-TNFα agent. Safety was comparable across therapies.

Implications for managed care pharmacy

This systematic review explores the real-world effectiveness and safety of biologic therapies for moderate-to-severe ulcerative colitis. Vedolizumab and tofacitinib were the most assessed therapies, with higher remission rates observed for tofacitinib compared with vedolizumab and for vedolizumab compared with anti-TNFα. Tofacitinib and ustekinumab showed comparable outcomes for steroid-free clinical remission. The safety profiles of all the therapies were comparable in real-world scenarios. These findings offer valuable guidance for health care providers in optimizing treatment decisions for patients with ulcerative colitis.

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ABSTRACT

BACKGROUND: Effectiveness and safety of advanced therapies for ulcerative colitis (UC) warrant assessment in the real world.

OBJECTIVE: To perform a systematic review and summarize real-world evidence of advanced therapies approved for moderate-to-severe UC.

METHODS: A systematic literature review was conducted using real-world studies of biologics or small molecules in UC using Embase, MEDLINE, and MEDLINE-In Process databases. Only products approved in any jurisdiction during the search were included. English-language full-papers (January 2005 to February 2022) and congress abstracts (January 2019 to February 2022) were included. Studies with less than 30 patients or only biologic-naive patients were excluded.

RESULTS: A total of 139 studies were included out of 3,930 identified articles (75%, published between 2019 and 2022; 64%, retrospective observational; 53%, from 5 countries [Italy, United States, Spain, United Kingdom, and Belgium]). Most studies were single agent (highest: vedolizumab = 50, tofacitinib = 24, and adalimumab = 18), and rates of clinical remission (CR) and adverse events varied widely. From the published comparative effectiveness studies (16), the rates of CR were numerically higher with vedolizumab vs anti-tumor necrosis factor (TNF)-α agents. Compared with vedolizumab, the effectiveness of tofacitinib was numerically greater in CR (occasionally significant). Rates of steroid-free CR were comparable between ustekinumab and tofacitinib. Infliximab was the most effective anti-TNFα agent, as reported by 2 studies. Remarkably, adverse events were similar across therapies in comparative studies.

CONCLUSIONS: Vedolizumab and tofacitinib were the most assessed therapies. In comparative studies, remission rates were numerically higher with tofacitinib vs vedolizumab and for vedolizumab vs anti-TNFα. Tofacitinib was comparable with ustekinumab

ABSTRACT *continued*

for steroid-free CR. Safety was comparable across therapies. Future studies should explore the literature gaps identified, including limited comparative studies with small sample sizes, variations in study designs and patient characteristics, varied definitions of CR, and limited use of patient-reported outcome measures in real-world settings.

Ulcerative colitis (UC) is a chronic inflammatory disease of unknown etiology that results in mucosal inflammation and ulceration of the colon. Many patients with UC experience frequent flares and hospitalizations, leading to a significant direct and indirect economic burden.[1-4] The primary therapeutic goal in UC is to induce and maintain clinical, endoscopic, and steroid-free remission (SF-REM) in the long term.[5,6]

The disease is classified as mild, moderate, or severe based on its clinical presentation.[2] The most commonly used criteria for defining moderate-to-severe UC include a total Mayo Clinic Score between 5 and 12, a rectal bleeding subscore (RBS) of at least 1, and a Mayo Clinic Endoscopic Score of at least 2.[3,4] Several advanced therapies (ATs) are approved for patients with moderate-to-severe UC, including biologics such as tumor necrosis factor (TNF)-α antagonists (infliximab, adalimumab, and golimumab), interleukin-12/23 antagonist (ustekinumab) and a recent interleukin-23 antagonist (mirikizumab), anti-integrin agent (vedolizumab), and small molecules *viz* Janus-Kinase inhibitors (tofacitinib, filgotinib, and upadacitinib) and sphingosine 1-phosphate receptor modulator (ozanimod, and recently also etrasimod).[7,8-11]

Real-world evidence (RWE) is gaining importance in clinical practice, whereas randomized controlled trials (RCTs) are considered the gold standard for demonstrating the efficacy and safety of drugs. The generalizability of RCT's findings remains an issue because of strict eligibility criteria, which render the patients unrepresentative of the heterogeneous population treated in routine clinical practice. RWE is derived from data sources, such as electronic health records, health surveys, and patient registries, and covers real-life information on treatment/patient pathways, health outcomes, and safety.[12,13] However, the variability in the study designs and execution significantly limits conclusions drawn from such data.

Although an increasing number of ATs have become available for the treatment of moderate-to-severe UC, a comprehensive assessment of their effectiveness and safety in a real-world setting is limited. We sought to systematically review and summarize published RWE on the effectiveness and safety of ATs for moderate-to-severe UC.

Methods

DATA SOURCES AND SEARCHES

A systematic literature review (SLR) was conducted following the standards published by the Cochrane Collaboration[14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[15] We performed a comprehensive literature search using Embase and MEDLINE databases through the Embase.com platform from January 1, 2005, to February 28, 2022. The MEDLINE Epub ahead of print, in-process, and nonindexed citations were searched on PubMed (February 28, 2022). The time frame was determined based on the first approval of infliximab in September 2005. Only products that were approved in any jurisdiction globally at the time of search were included. Supplementary Tables 1-3, available in online article, provide the details of the search strategy. Searches were limited to English-language articles published in 2005 and later for full-text publications, and from January 2019 to February 2022 for conference abstracts.

STUDY SELECTION CRITERIA

Supplementary Table 4 provides the details of the inclusion and exclusion criteria (population, interventions/ATs, outcomes, study design, and time period). Studies were included if they had adult patients with moderate-to-severe UC, with prior exposure to biologics or mixed populations, and reported effectiveness and/or safety outcomes using a real-world observational study design (retrospective or prospective). Studies with less than 30 patients or only biologic-naive patients were excluded. Non-English articles or those published before 2005 were excluded. All the retrieved citations were screened by 2 reviewers as per predefined eligibility criteria and a third reviewer resolved the discrepancies by consensus after discussion. Data extraction was conducted from full-text publications. Multiple publications from the same study were linked and extracted as a single study. The PRISMA flow diagram is provided as Supplementary Figure 1.

DATA EXTRACTION AND QUALITY ASSESSMENT

Data extraction and quality checks were performed by individual reviewers; differences were reconciled by the third reviewer. Data on study characteristics and methods, patient and treatment characteristics, follow-up duration, time points of assessments, effectiveness outcomes, safety events, results, and conclusions were extracted into a Microsoft Excel spreadsheet. Included studies were critically appraised for methodological quality using the Newcastle–Ottawa Scale. The Newcastle–Ottawa Scale is a tool for assessing the quality of nonrandomized studies

using a star system to evaluate selection, comparability, and outcome reporting.[16] Data were analyzed qualitatively, and results are reported as numbers and/or percentages or as crude median, Q1, and Q3.

Results

A total of 3,930 records were identified. Of these, 3,066 were excluded during title and abstract screening, and 864 full-text publications were evaluated for inclusion. After full-text screening, 181 publications were included. A total of 139 distinct studies were included for data extraction and analysis after linking multiple publications from the same studies (Supplementary Figure 2A-B; Supplementary Table 5).

QUALITY OF STUDIES

According to the Newcastle–Ottawa Scale,[16] studies were scored from 0 to 9 stars. The quality scores for included studies ranged from 2 to 8 stars, with most studies (69%) assigned a rating of 6 or more, indicating good quality. Conference abstracts were generally rated lower. All comparative studies were assigned 5 or more stars, and 10 studies were given 7 or 8 stars (Supplementary Table 6).

DESCRIPTION OF THE INCLUDED STUDIES

Among eligible included studies, 109 (78%) were full-text publications and 30 (22%) were conference abstracts; their information is provided in Supplementary Table 7. Most of the studies (75%) were published between 2019 and 2022, and 53% were from 5 countries (Italy, n = 23; United States, n = 19; Spain, n = 12; United Kingdom, n = 10; Belgium, n = 9). Sixty-four percent of studies were retrospective, and 33% were prospective observational in nature. Studies were predominantly (67%) multicenter. Data sources used included electronic medical/health/hospital records (75%), registries (12%), chart reviews (9%), claims databases, and global safety databases (2% each).

PATIENT CHARACTERISTICS

Across studies, the median age of patients ranged from 26[17] to 55[18] years (median [Q1, Q3]: 41 [39, 45.5] years). The proportion of male patients ranged from 25%[19] to 73%,[20] with 46% of studies having an equal or almost equal balance of sexes. Median body mass index ranged from 21[21-23] to 27[24] kg/m^2 (median [Q1, Q3]: 24.5 [24, 25] kg/m^2) in the 45 studies. Eighty-two percent of studies reported a duration of disease between 4 and 9 years (range: 2[25-26] -12[27] years [median (Q1, Q3): 7 (5, 8.5) years]). The extent of disease (E1/E2/E3) was distributed as up to 20% of patients with E1 (proctitis [Proximal extent to the sigmoid colon]; median [Q1, Q3]: 6% [3%, 11%]), 21% to 50% with E2 (left-sided colitis [to the splenic flexure]; 37% [31%, 42%]), and more than 51% patients with E3 (extensive colitis [beyond the splenic flexure]; 56% [46%, 63%]) (Supplementary Table 7). Patient's characteristics are presented in Figure 1.

Thirteen percent of studies had only biologic-exposed patients, 63% had more than 50% biologic-exposed patients, and 28% presented subgroup analyses for biologic-exposed patients. Of the biologic-exposed cohort, most patients had prior exposure to anti-TNFα agents in the range of 11%-100%, with a median (Q1, Q3) of 66% (44%, 94.2%). Other studies described patients previously treated with biologics such as vedolizumab, ustekinumab, and tofacitinib. Within these studies, the proportion of exposed patients varied (vedolizumab [median, 72% (57%, 81.5%); range, 2%-100%]; ustekinumab [median, 5% (3%, 8.5%); range, 1%-18%]; tofacitinib [median, 20% (8%, 30.7%); range, 10%-33%]).

INTERVENTIONS/ATs

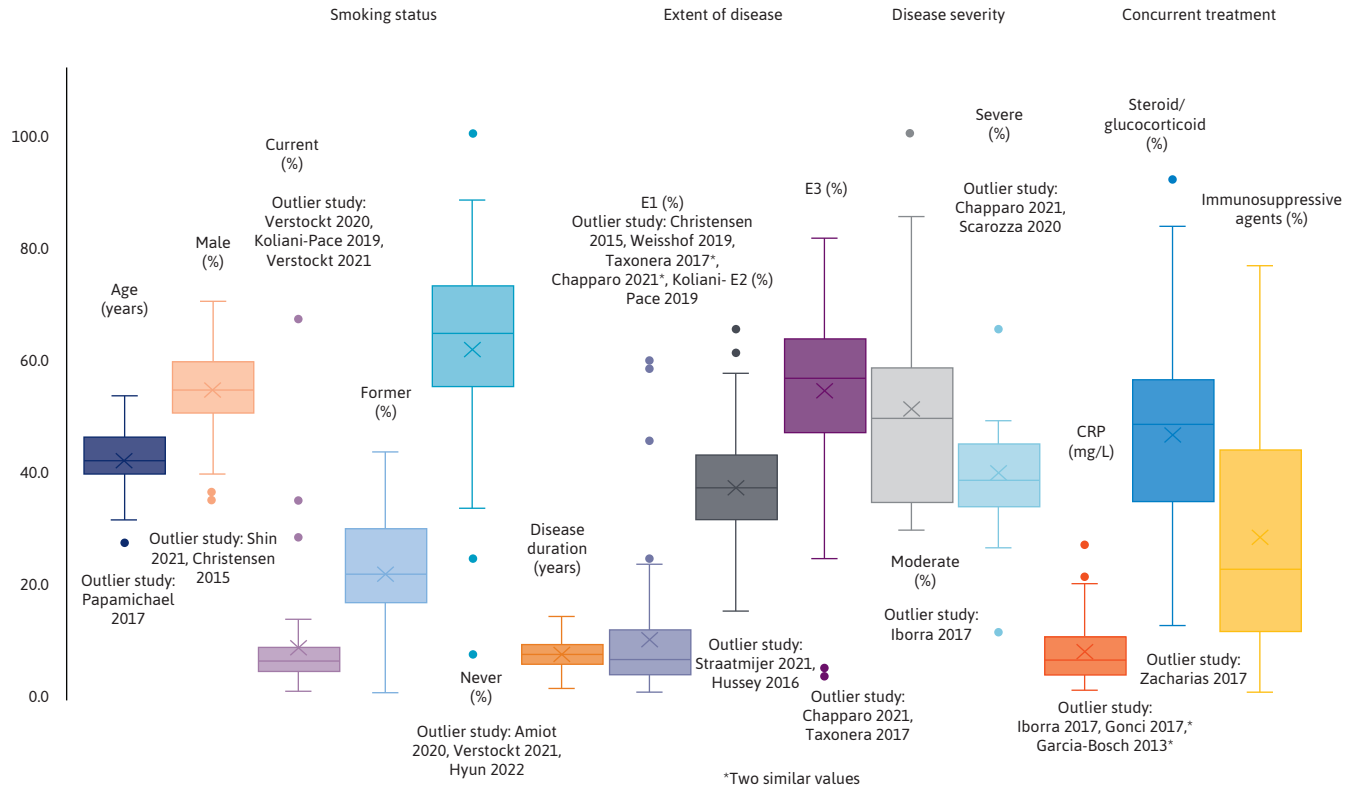
Eighteen studies were comparative [18,19,23,24,27-40] (vedolizumab vs anti-TNFα agents[18,28-36] [n = 10]; tofacitinib vs vedolizumab[23,27,37,38] [n = 4]; different anti-TNFα agents[19,24,39] [n = 3]; tofacitinib vs ustekinumab[40] [n = 1]), whereas 121 were single-arm studies (vedolizumab [n = 50], tofacitinib [n = 24], adalimumab [n = 18], golimumab [n = 14], infliximab [n = 10], ustekinumab [n = 5]). No real-world studies were yet found for filgotinib or ozanimod.

FOLLOW-UP AND OUTCOMES

In 76% of studies, the mean/median duration of follow-up was up to 54 weeks. Effectiveness outcomes were most frequently reported at 8-16 weeks, followed by 48-54 weeks; outcomes beyond 54 weeks were usually not reported. Clinical response (CRES), clinical remission (CR), SF-REM, and endoscopic remission were the most commonly reported outcomes, whereas histologic remission, patient-reported outcomes (PROs), and deep remission (combined clinical and endoscopic remission) were rarely reported. Primary nonresponse or loss of response was reported in 42 studies. Any adverse event (AE) (46%), UC-related colectomy/surgery (46%), discontinuation/withdrawal because of AE (37%), and infections (24%) were frequently reported safety outcomes. Major adverse cardiovascular events (MACEs), malignancies, and venous thromboembolism (VTE) were reported in 12% of studies.

Within studies reporting CR, the Partial Mayo Score (PMS) or total Mayo Clinic Score of less than or equal to 2 alone or combined with RBS and stool frequency subscore (SFS) of less than 1 were the most used definitions, followed by a PMS of less than or equal to 1, or Simple Colitis Clinical Activity Index (SCCAI) score of less than or equal to 2. SF-REM was reported as CR achieved without the use of

FIGURE 1 Patient Demographic and Clinical Characteristics at Baseline



The weighted median and interquartile ranges (Q1, Q3) were calculated from the aggregated values reported in the individual studies. Data presented as box plots show minimum. Age, duration of disease, and CRP are continuous data.

CRP = C-reactive protein; E1, E2, and E3 are extent of disease; Q1, median, Q3, and maximum values of each parameter. Q1 = first quartile; Q3 = third quartile.

steroids. Of the studies reporting endoscopic remission and mucosal healing (MH), a Mayo Endoscopic endoscopic subscore of 1 or 0 was the most commonly used definition; however, a few studies included histological remission in their definition of MH (Figure 2A). Few studies reported deep remission, usually defined as a combination of CR and endoscopic remission/MH (Figure 2B).

RWE ON EFFECTIVENESS

Single-Treatment Studies

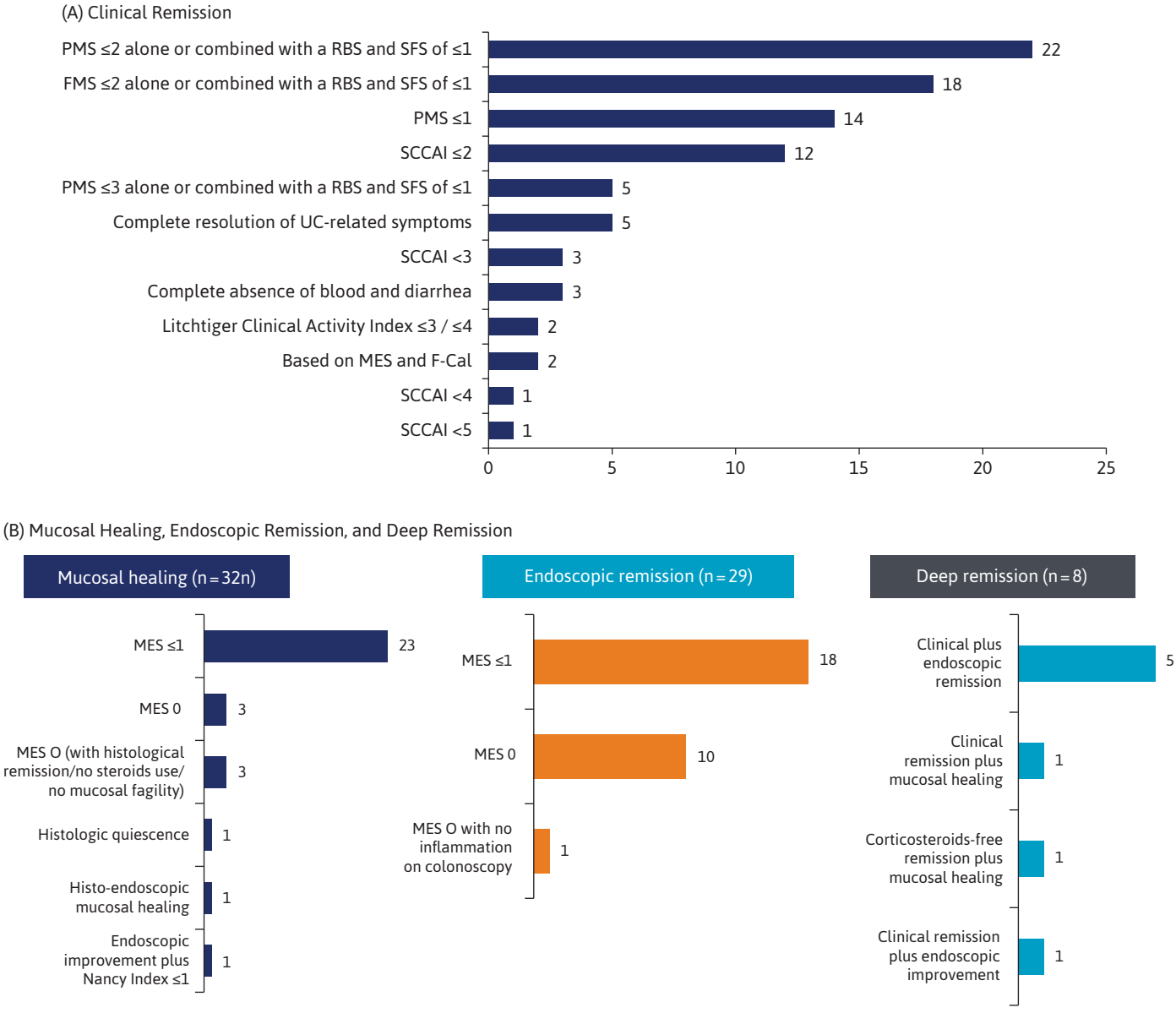
Vedolizumab. We identified 50 real-world studies of vedolizumab. The proportion of patients who achieved CR with vedolizumab after induction ranged from 18%[22] to 87%[41] at 8-12 weeks, and 32%[42] to 56%[43] at 14 weeks after initiation. CR was reported to be maintained in 36%[44] to 71%[45] of patients at 24 weeks and 28%[46] to 77%[45] at 52-54 weeks. Long-term CR was reported in 28%[46,47] to 33%[48] of patients at 104-108 weeks (Supplementary Figure 3).

Tofacitinib. In the 24 studies describing the use of tofacitinib, rates of CR varied between 23%[49] and 57%[50] at 8 weeks and 32%[51] and 65%[52] at 16 weeks. CR was maintained in 23%[17] to 62%[53] of patients at 24-26 weeks and 27%[54] to 64%[55] of patients at 48-52 weeks or more. One study with long-term data reported 56%[56] of patients achieving CR at 78 weeks and 54%[56] to 70%[50] at 104 weeks (Supplementary Figure 4).

Ustekinumab. The CR varied from 35%[57] to 43%[55] in a few studies[55,57,58] at 12-16 weeks. One study reported 39%[57] of patients achieving CR at 24 weeks, whereas 3 studies reported 33%[57] to 45%[55] of patients achieving CR at 52 weeks. (Supplementary Figure 5).

Anti-TNFα Agents. Forty-two studies were included for anti-TNFα agents (18 adalimumab, 14 golimumab, and 10 infliximab). In the single-arm studies of anti-TNFα agents, CR was ranging 16%[59] to 65%[60] at 8-14 weeks (induction), 27%[61] to 86%[62] at 24-30 weeks, and 20%[59] to 90%[62] at 52-54 weeks

FIGURE 2 Number of Studies Following Definitions



F-Cal = fecal calprotectin; FMS = Full Mayo Score; MES = Mayo Endoscopic Subscore; PMS = Partial Mayo Score; RBS = Rectal Bleed Subscore; SCCAI = Simple Colitis Clinical Activity Index; SFS = Stool Frequency Subscore; UC = ulcerative colitis.

(maintenance). The long-term CR reported in studies varied greatly, with 25%[63] to 68%[64] of patients achieving this endpoint at 64-156 weeks (Supplementary Figure 6).

Comparative Studies

Vedolizumab vs Anti-TNFα Agent. Ten studies compared vedolizumab with anti-TNFα agents[18,28-36] and 3 of these were propensity-scored matched (PSM) comparisons.[18,28,30] The PSM analysis from a study with 722 patients (454 vedolizumab, 268 anti-TNFs) showed that vedolizumab-treated patients were more likely to achieve CR (hazard ratio [HR] = 1.651; 95% CI = 1.229-2.217), SF-REM (HR = 1.828; 95% CI = 1.135-2.944), and steroid-free deep remission (HR = 2.819; 95% CI = 1.496-5.310) than those treated with anti-TNFα agents.[28] Another study reported that rates of SF-REM in

TABLE 1 A Summary of Comparative Effectiveness Reported in Studies Comparing Vedolizumab vs Anti-TNFα Agents

Outcome	Study name	Follow-up (weeks)	Vedolizumab	IFX	GOL	ADA	Anti-TNFα as class
Clinical remission	Lukin 2022[28]	48	42% (187/453)[a]	37% (61/163)			
	Helwig 2020[31]	26	54%[b] (*P* = 0.0380)				32%[b]
	Bertani 2020[32]	54	75%	44%	61%	65%	
	Davis 2019[34]	12	48% (NS)				IFX/ADA/GOL: 40%
		24	52% (NS)				IFX/ADA/GOL: 39%
		52	**51%**				IFX/ADA/GOL: 28%
Clinical response	Gagnon 2021[29]	52	48% (19/39)	63% (45/68)		57% (33/58)	
	Macaluso 2020[18]	12	71%		68%	69%	
		52	72% (*P* < 0.001 vs GOL, ADA)		40% (NS vs ADA)	48% (*P* < 0.001)	
	Davis 2019[34]	12	57% (NS)				IFX/ADA/GOL: 55%
		24	69% (NS)				IFX/ADA/GOL: 59%
		52	51% (NS)				IFX/ADA/GOL: 42%
Steroid-free clinical remission	Macaluso 2020[18]	12	24% (NS vs GOL, ADA)		31% (NS vs ADA)	33%	
		52	52% (*P* = 0.001 vs GOL; *P* = 0.002 vs ADA)		29% (NS vs ADA)	31%	
	Davis 2019[34]	12	33% (NS)				IFX/ADA/GOL: 31%
		24	48% (NS)				IFX/ADA/GOL: 36%
		52	14% (NS)				IFX/ADA/GOL: 25%

Significant values are highlighted in bold.

[a]*Vedolizumab was shown to be associated with a higher probability of achieving clinical remission compared with infliximab (hazards ratio = 1.810; 95% CI = 1.225-2.675).*

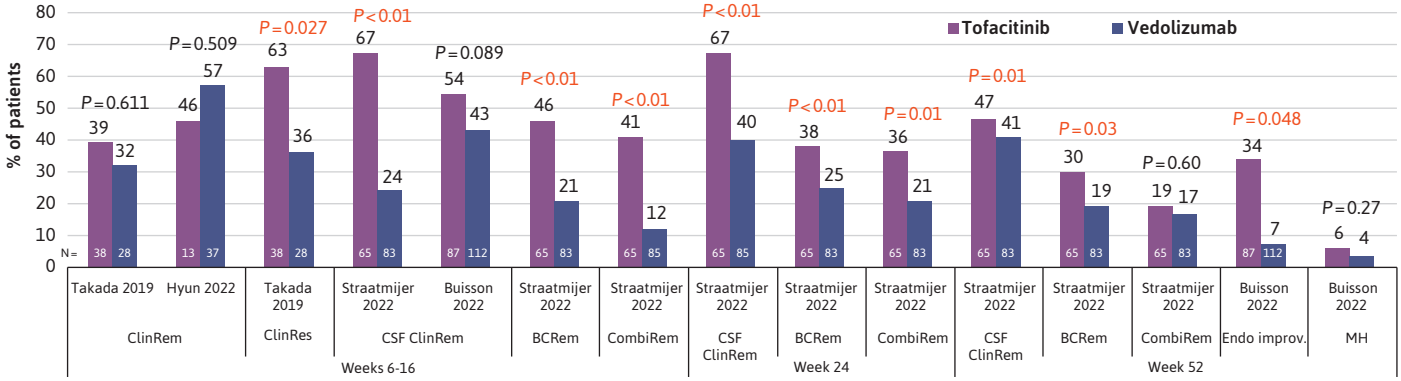
[b]*Cumulative rates estimated using nonparametric, stratified K-M approach to account for variability in patient follow-up and timing of outcome events.*

ADA = adalimumab; GOL = golimumab; IFX = infliximab; NS = nonsignificant; S = significant; TNFα = tumor necrosis factor α.

vedolizumab, adalimumab, and golimumab-treated patients were similar at 12 weeks but were significantly greater with vedolizumab at 52 weeks (52%, 31%, and 29%, respectively; $P \leq 0.002$).[18] In a multicenter chart review study from Germany (vedolizumab, n = 76; anti-TNFα, n = 57), the rates of CR at week 26 were numerically higher with vedolizumab vs anti-TNFα agents (54% vs 32%).[31] Comparable rates of CRES, CR, and SF-REM between vedolizumab and anti-TNFα agents at 6, 24, and 52 weeks, respectively, were reported in a United Kingdom study (Table 1).[34]

Tofacitinib vs Vedolizumab. Four studies compared tofacitinib with vedolizumab,[23,27,37,38] and among them including a prospective study from the Initiative on Crohn and Colitis registry with 65 patients on tofacitinib and 83 on vedolizumab, previously exposed to anti-TNFα. PSM results showed that tofacitinib-treated patients were more likely to achieve SF-REM (ie, SCCAI ≤2) compared with vedolizumab-treated patients at week 12 (odds ratio [OR] = 6.33, 95% CI = 3.81-10.50, $P < 0.01$), week 24 (OR = 3.02, 95% CI = 1.89-4.84, $P < 0.01$), and week 52 (OR = 1.86, 95% CI = 1.15-2.99, $P = 0.01$). Biochemical remission (C-reactive protein ≤5 mg/L or fecal calprotectin ≤250 μg/g) was also more frequently reported in tofacitinib-treated patients vs vedolizumab ($P \leq 0.03$).[27] A multicenter study from France with 87 patients receiving tofacitinib and 112 administered with vedolizumab, previously exposed to at least 1 anti-TNFα, described that 16-week SF-REM was numerically greater with tofacitinib than vedolizumab (54% vs 43%). The rates of 16-week SF-REM were numerically higher with tofacitinib after 1 (57% vs 51%, $P = 0.77$), 2 (55% vs 42%, $P = 0.61$), and at least 3 biologics (57% vs 6%, $P = 0.007$). Tofacitinib was more effective than vedolizumab in achieving SF-REM in patients with primary failure to at least 1 biologic (72% vs 31%, $P = 0.049$). Endoscopic improvement was more common in patients treated with tofacitinib (34% vs 7%, $P = 0.048$).[38] In a single-center retrospective study from Japan in patients with UC who initiated tofacitinib (n = 38) and vedolizumab (n = 28), the rate of CR (ie, PMS ≤1 or decrease from baseline by ≥3 points) at week 6 was significantly higher with tofacitinib than vedolizumab (63% vs 36%, $P = 0.027$) (Figure 3).[37]

FIGURE 3 A Summary of Comparative Effectiveness Reported in Studies Comparing Tofacitinib vs Vedolizumab



BCRem was defined as a CRP ≤5 mg/L or F-Cal ≤250 µg/g.

BC = biochemical remission; ClinRem = clinical remission; ClinRes = clinical response; CSF = corticosteroids-free; CombiRem = combined CSF ClinRem and BCRem; MH = mucosal healing.

Comparison Between Anti-TNFα Agents. Of the 3 studies comparing anti-TNFα agents,[19,20,39] only 2 reported effectiveness.[19,39] A single-center retrospective study from Italy comparing 3 anti-TNFα agents (infliximab, adalimumab, and golimumab) showed that overall CRES was 77% after induction, 81% at 30 weeks, and 77% at 52 weeks. The SF-REM was 40%, 46%, and 55% after induction, 30 and 52 weeks, respectively. The rates of CRES, CR, and SF-REM were greater with infliximab at all the time points compared with adalimumab and golimumab.[20] The rate of treatment failure was higher (after induction), and rates of CRES and SF-CR (at the end of follow-up) were lower with golimumab at week 14 compared with infliximab and adalimumab.[19] A multicenter study extracting web-based data from the Sicilian Network for inflammatory bowel disease compared adalimumab (n = 118) and golimumab (n = 79) in moderate-to-severe patients with UC, with 50%-63% of patients in each group previously exposed to biologics. PSM analysis showed that clinical benefit (ie, CRES plus SF-REM) was significantly higher with adalimumab than golimumab after 8 weeks (79% vs 63%, P = 0.026) and at the end of follow-up (median 34-40 weeks) (67% vs 47%, P = 0.008).[39]

Tofacitinib vs Ustekinumab. A single study from the United States was identified comparing tofacitinib with ustekinumab, which was conducted in biologic-experienced patients with UC (45 tofacitinib and 36 ustekinumab).[40] The PSM results showed similar rates of SF-REM (ie, SCCAI ≤2 [44% tofacitinib vs 40% ustekinumab, P = 0.82]) and steroid-free CRES (46% tofacitinib vs 49% ustekinumab, P = 1.00) at 12-16 weeks, and SF-REM (60% tofacitinib vs 55% ustekinumab) at 52 weeks, after treatment initiation.[40]

RWE ON SAFETY

Single-Treatment Studies

Vedolizumab. A 4-year postmarketing safety data analysis on vedolizumab reported serious AEs (SAEs) in 10% of patients with UC. Most frequent AEs were gastrointestinal events (17%), infections (7%), and malignancies were reported in less than 1% of patients.[65]

Other real-world studies showed a wide proportion of patients reporting AEs (2%[66] to 62%[67]) and SAEs (2%[68] to 17%[48]). UC-related hospitalization ranged from 4%[69] to 22%.[25] The rate of colectomy varied between 1%[69-71] and 26%,[47] infections between 1%[72] and 22%,[67] whereas the serious infections were infrequent (3%-4%).[44,48,73] Herpes-zoster virus (HZV) infection, VTE, and MACE were not reported in vedolizumab studies. Malignancy rates were low (Supplementary Table 8).[48,67] Discontinuation rate reported varied between 8%[74] and 51%[75] at at least 52 weeks.

Tofacitinib. A safety study of tofacitinib in patients with UC (27 months reporting period; 8,916 person-years [PYs] exposure) showed that reported AEs were consistent with those seen in RCTs and mostly were nonserious.[76] Overall, 4,226 case reports were received and included 12,103 AEs, of which 1,839 were SAEs (27%; death: 0.4%). The reported incidence rate for gastrointestinal disorders, infections and infestations, and vascular disorders was 6.97, 3.28, and 1.26 per 100 PYs, respectively.[76]

AEs in single-arm studies ranged widely between 9%[77] and 72%,[78] and SAEs ranged between 5%[56] and 16%.[79] UC-related hospitalization was reported in 1%[80] to 19%[77] and UC-related colectomy ranged between 1%[52] and 26%.[79] Infections were

reported in 3%[51] to 24%,[79] whereas information on serious infections was not reported commonly (HZV infection was reported in up to 8% of patients).[17,50,51,56,79] The incidence rate of VTE was negligible less than or equal to 1%,[17,50,51,53,56,78,81,82] whereas MACEs and malignancies were rarely reported and had a very low incidence (Supplementary Table 9).[17,50,51,54,79,83] The discontinuation rate ranged between 31%[56] and 61%[83] at at least 52 weeks.

Ustekinumab. AEs were reported in 1%[84] to 12%,[55,57,58,84,85] whereas SAEs occurred in 4%[85] to 6%.[55] The rate of UC-related hospitalization was 3%[85] to 6%,[55] and colectomy rates varied between 2%[85] and 9%.[57] The infections were reported in 6%,[55] although serious infections were infrequent. HZV infection, VTE, or malignancies were not reported. The rates of MACE were very infrequent (1% in one study[85]; Supplementary Table 10), and the discontinuation rate was reported to be between 13%[84] and 36%[57] at at least 52 weeks.

Anti-TNFα Inhibitors. Reports of AEs varied between 4%[61,86] and 38%[87] (infliximab = 6%[64] to 27%[87]; adalimumab = 4%[61,86] to 38%[87]; golimumab = 8%[88] to 22%[88]) and 0%[88] and 11%[89] for SAEs (infliximab = 4%[64] to 11%[90]; adalimumab = 3%[91] to 5%[92]; golimumab = 0%[88] to 5%[88]). Colectomy rates were between 0%[20] and 36%[63] (infliximab = 1%[26] to 36%[63]; adalimumab = 3%[93] to 25%[94]; golimumab = 0%[20] to 22%[95]), whereas UC-related hospitalizations were not commonly reported. Patients reporting infections in anti-TNFα agent studies ranged from 0%[20] to 47%[96] (adalimumab = 2%[93] to 47%[96]; golimumab = 3%[97] to 8%[88]), and serious infections varied between 0%[61] and 6%[26,91] (infliximab = 2%[87] to 6%[26]; adalimumab = 0%[61] to 6%[91]; with golimumab = 2%[88]). HZV infection (1%[87] to 3%[96]) and malignancies (0%[61] to 3%[96]) were very low. VTE and MACE were reported infrequently (Supplementary Table 11A-C). The discontinuation rate varied between 7%[98] and 84%[63] at at least 1 year.

Comparative Studies

Vedolizumab vs Anti-TNFα Agent. The safety events comparing vedolizumab and anti-TNFα agents are summarized in Supplementary Table 12. Most studies were descriptive, only reporting the proportion of patients with safety events. No statistically significant differences were reported for the risk of SAEs (HR = 0.899; 95% CI = 0.502-1.612) or serious infections (HR = 1.235; 95% CI = 0.608-2.511) between vedolizumab-treated (n = 454) and anti-TNFα–treated (n = 268) patients.[28]

Tofacitinib vs Vedolizumab. Two descriptive studies (one each from Korea[23] and Japan[37]) reported that safety profiles of tofacitinib and vedolizumab were similar in terms of overall AEs, with no reported SAEs (Supplementary Table 13). A study by Straatmijer et al using inverse probability of treatment weighing showed that vedolizumab-treated patients (n = 83) had an overall higher chance of experiencing AEs than tofacitinib-treated (n = 65) patients (OR = 1.83; 95% CI = 1.10-3.03; *P* = 0.02), although the number of severe AEs were similar between the 2 treatment groups (OR = 0.39; 95% CI = 0.03-4.33; *P* = 0.44).[27]

Comparison Between Anti-TNFα Agents. Safety events did not differ significantly across anti-TNFα agents. A study by Barberio et al reported a similar and generally good safety profile for adalimumab, golimumab, and infliximab (originator and biosimilar).[19] Hoque et al described the 8% colectomy rate within 12 months following treatment with each of golimumab (87 patients) and adalimumab (96 patients).[24] There were reports of 10 AEs in the adalimumab group with an incidence rate of 80.4/1,000 PYs and 4 AEs in the golimumab group with an incidence rate of 33.1/1,000 PYs. The difference between the 2 groups was not statistically significant (*P* = 0.247).[39]

Tofacitinib vs Ustekinumab. In a study comparing tofacitinib (45 patients) with ustekinumab (36 patients), AEs were comparable between tofacitinib (11%) and ustekinumab (11%; 6%, respectively). Infection, deep vein thrombosis, liver injury, refractory nausea/vomiting, and shingles were reported with tofacitinib, whereas rash and urinary tract infection were reported with ustekinumab. Drug discontinuation or total colectomy was reported in 51% and 36% for tofacitinib and ustekinumab, respectively.[40]

Discussion

Real-world data provide valuable evidence and insight to support the efficacy and tolerability of therapies observed in RCTs; trial patients represent only a proportion of the entire UC population in contrast to studies performed in real-world settings.[99] Overviews of recently available ATs in patients with moderate-to-severe UC may be helpful to address this gap. Currently available SLR and meta-analyses for vedolizumab,[100] tofacitinib,[101,102] or ustekinumab[103] primarily assessed evidence from single-arm studies. These studies are limited with smaller sample sizes and limited outcomes assessed. Our review provides a comprehensive qualitative overview of RWE on the effectiveness and safety of ATs, incorporating data from both peer-reviewed full-text manuscripts/articles and conference abstracts.

In this SLR, more than half of real-world studies originated from 5 countries, namely the United States, United Kingdom, Italy, Spain, and Belgium. The findings may be an overestimate because of the exclusion of non-English studies from the analysis. Vedolizumab and tofacitinib were the most frequently assessed/reported ATs in moderate-to-severe UC, whereas the RWE for ustekinumab in UC is limited. Ozanimod and filgotinib were recently approved; hence, RWE

was not yet available during the time of literature search.[10] Additionally, mirikizumab, upadacitinib, and etrasimod were not approved[11] at the time of searches for this review.

There was a wide variation in the studies in terms of their design, sample size, follow-up duration, patient demographics and characteristics, disease duration, previous exposure to biologics, and outcomes assessed. Although CR was the most reported outcome,[6,7] a marked variability was observed in the definition of CR across studies. A possible explanation may be the evolution of study endpoints in RCTs and subsequently in real-world analyses. Common definitions included a PMS of less than or equal to 2 either alone or combined with an RBS and SFS of less than or equal to 2, a PMS of less than or equal to 1, or a SCCAI less than or equal to 2. Considering these variations, we feel that a uniform criterion of CR would be helpful to enhance comparability across studies. We suggest using a PMS of less than or equal to 2 and no individual score greater than 1 and RBS of 0 or the PRO2 criterion in future studies, which is also aligned with the definition used in current RCTs.

A few comparative studies were included in this review, most of which had a short follow-up time. Overall, the rate of CR with tofacitinib was numerically higher than vedolizumab and comparable with ustekinumab. Clinical remission was numerically higher for vedolizumab vs anti-TNFα agents. These results should be interpreted cautiously because of the small sample sizes in these studies and marked variation in the baseline characteristics of the patients, although a few studies reported PSM comparisons.[18,27,28,30,39,40] Comparative studies with PSM analysis are strongly suggested for future research.

European Medicines Agency guidance (2018) on the development of new treatments for UC stated that only patients with MH (ie, absence of macroscopic signs of active inflammation) and no, or very mild, symptoms and signs should be considered in remission.[104] The guidelines released by the American College of Gastroenterology and the American Gastroenterological Association recommend the use of SF-REM as a marker of remission in patients with UC.[6,105] However, a recent ECCO position paper and the STRIDE II guidelines have also placed emphasis on histological activity, which can persist despite clinical and endoscopic remission and is a known risk factor for disease flare. Histological remission (ie, the absence of inflammation and ulceration/erosion) is now under discussion as a target for UC therapy,[106,107] however, it is rarely reported in the studies we reviewed for this SLR.[39,55,83,108] Histological healing may be associated with improved clinical outcomes; therefore, it should be considered as an outcome in future real-world studies.

This SLR also highlighted that the use of PRO measures, apart from disease activity, was very limited in real-world studies. The literature indicates less use of PROs in phase 4 or observational studies compared with RCTs.[109,110] PROs provide valuable insights on the experience of their therapies.[111] The European Medicines Agency guidance and the STRIDE II guidelines also suggest that a symptomatic relief is best evaluated by PROs.[104,107] Therefore, the use of PROs in RWE studies should be encouraged. This can be facilitated in several ways, including the development of standards for their use, collection, and analysis.[112,113]

There are considerable variations in AE and SAE reporting in single-arm studies. Comparative studies reported similar safety event rates across ATs, although most studies had small sample sizes and/or were not adjusted for covariates. There were zero or limited occurrences of MACE[50,54,79] and malignancies.[55,61,67,83,85]

LIMITATIONS

There are limitations to this SLR conducted on real-world studies as the data collection is less stringent than RCT. The differences in study designs and patient characteristics across studies may result in considerable heterogeneity in reported outcomes. Thus, outcomes should be interpreted with caution if a quantitative assessment of heterogeneity was not performed. Some studies had small sample sizes, including those comparing tofacitinib with ustekinumab or vedolizumab. Only studies published in the English language were included; this may be considered a source of bias, although most articles are published in English. Despite these limitations, this SLR reports a large volume of RWE on the effectiveness and safety of ATs in moderate-to-severe UC, and the utility of this RWE in decision-making should not be underestimated.

Conclusions

This review comprising 139 real-world studies of ATs in moderate-to-severe UC highlights vedolizumab and tofacitinib as the most assessed ATs. Most studies (87%) assessed a single agent. The proportion of patients with CR and AEs varied widely., In comparative studies with largely bioexposed patients, CR rates were numerically higher with tofacitinib vs vedolizumab and comparable with ustekinumab. The CR was numerically higher for vedolizumab vs anti-TNFα agents. Generally, the safety events were similar across ATs. Several evidence gaps at the time of search were identified, such as the paucity of comparative studies, small sample sizes, variations in study design, patient characteristics, and definition of outcomes, limited use of PRO measures, and limited reporting of AEs such as MACE and malignancies. Further research should focus on addressing these issues.

DISCLOSURES

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DATA AVAILABILITY

All relevant data underlying this article are available in the article and in its online Supplementary Materials.

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