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SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Comparative Risk of Serious Infections With Biologic Agents and Oral Small Molecules in Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis

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Risk of serious infections with advanced therapies for IBD

Meta-analysis of 20 head-to-head studies

Ustekinumab vs. TNFα antagonists (5 cohorts; 23,232 patients)	Vedolizumab vs. TNFα antagonists (17 cohorts; 51,596 patients)	Ustekinumab vs. vedolizumab (5 cohorts; 1,420 patients)
• **CD**: **51% lower risk** of serious infections with ustekinumab • **UC**: Knowledge gap	• **CD**: **No difference** in risk of serious infections (OR, 1.03) • **UC**: **32% lower risk** of serious infections with vedolizumab	• **CD**: **60% lower risk** of serious infections with ustekinumab • **UC**: Knowledge gap

Safety profile of advanced therapies for IBD varies, and is influenced by treatment effectiveness and intrinsic immune suppression

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BACKGROUND & AIMS: **Safety is a key consideration when choosing advanced therapies (biologic agents and oral small-molecule inhibitors/modulators) in patients with inflammatory bowel diseases (IBDs). We performed a systematic review and meta-analysis comparing the risk of serious infections with advanced therapies in active comparator studies.**

METHODS: **Through a systematic search until February 28, 2022, we included 20 head-to-head studies comparing risk of serious infections with tumor necrosis factor α (TNFα) antagonists, vedolizumab, ustekinumab, tofacitinib, filgotinib, and ozanimod in patients with IBD. We performed random-effects meta-analysis comparing different advanced therapies.**

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Abbreviations used in this paper: CD, Crohn's disease; HR, hazard ratio; IBD, inflammatory bowel disease; IMM, immunomodulator; IQR, interquartile range; OR, odds ratio; RCT, randomized controlled trial; TNFα, tumor necrosis factor α; UC, ulcerative colitis.

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RESULTS: **No significant difference was observed in the risk of serious infections between vedolizumab vs TNFα antagonists in all patients with IBD (17 cohorts: odds ratio [OR], 0.84; 95% CI, 0.68–1.04), with moderate heterogeneity (I^2 = 37%); on subgroup analysis, vedolizumab was associated with a lower risk of serious infections in patients with ulcerative colitis (11 cohorts: OR, 0.68; 95% CI, 0.56–0.83; I^2 = 0%), but not in Crohn's disease (CD) (9 cohorts: OR, 1.03; 95% CI, 0.78–1.35; I^2 = 42%). Age, sex, prior biologic exposure, and use of biologic monotherapy did not influence this association. In patients with CD, ustekinumab was associated with a lower risk of serious infections vs TNFα antagonists (3 cohorts: OR, 0.49; 95% CI, 0.25–0.93; I^2 = 16%) and vs vedolizumab (3 cohorts: OR, 0.40; 95% CI, 0.17–0.93; I^2 = 67%). Few studies compared other advanced therapies.**

CONCLUSIONS: **Vedolizumab may offer net benefit over TNFα antagonists in patients with ulcerative colitis, but not in CD. Ustekinumab may offer net benefit over TNFα antagonists and vedolizumab in patients with CD.**

Keywords: Biologics; Risk-Benefit; Comparative; Propensity Score.

Over the past decade, the therapeutic armamentarium for the medical management of patients with moderate-to-severe inflammatory bowel diseases (IBDs) has expanded substantially.[1] Optimal positioning of these novel advanced immunosuppressive therapies requires a careful integration of the medication's effectiveness and safety, in the context of an individual patient's risk of disease- and treatment-related complications. Although recent head-to-head trials, network meta-analyses, and observational studies have examined the comparative effectiveness of different therapies for the management of patients with IBD,[2–6] there has been limited comparative assessment of the risk of serious infections with different advanced therapies including tumor necrosis factor α (TNF-α) antagonists, non–TNF-targeting biologic agents and oral small-molecule inhibitors/modulators such as Janus kinase inhibitors and sphingosphine 1–phosphate receptor modulators. In a prior systematic review, we systematically synthesized the comparative risk of serious infections with TNFα antagonists alone vs in combination with immunomodulators (IMMs) vs IMM monotherapy.[7] Besides identifying a higher risk of serious infections with TNFα antagonists vs IMM monotherapy, and a modestly higher risk with combination therapy vs TNFα antagonist monotherapy, we identified the lack of real-world comparative safety studies of novel non–TNF-targeting biologics as a key knowledge gap.[7–9]

Hence, we conducted a systematic review and meta-analysis focusing on comparing the risk of serious infections with novel advanced therapies such as non–TNF-targeting biologic agents and oral small-molecule inhibitors/modulators vs established TNFα antagonists. By focusing on head-to-head comparative studies, using TNFα antagonists as a common reference, we sought to minimize conceptual heterogeneity across studies to more optimally inform evidence. These data, combined with evidence on comparative effectiveness of therapies, can inform the net benefit of different advanced therapies in IBD.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and was conducted following a priori established protocol (available upon request).[10]

Selection Criteria

We included randomized controlled trials (RCTs) and cohort studies that met the following inclusion criteria: (1) patients: adult patients with IBD; (2) intervention: treatment with approved advanced therapies (TNFα antagonists, vedolizumab, ustekinumab, tofacitinib, filgotinib, or ozanimod); (3) comparator: alternative advanced therapies; (4) outcome: risk of serious infections; and (5) study design: only head-to-head or active comparator studies.

We excluded the following: (1) noncomparative studies (in which infection risk was reported in patients exposed vs not exposed to the medication of interest); (2) studies in which the comparator group included only mesalamine-treated patients (to avoid confounding by disease severity and focus analyses on patients with moderate–severe disease) or conventional IMMs (thiopurines and/or methotrexate) (because this was evaluated in our prior systematic review)[7]; (3) studies reporting the risk of any infection or opportunistic infections that did not meet the definition of serious infections, or those that focused only on specific infections (such as pneumonia or *Clostridiodes difficile*); and (4) studies performed in patients who did not have IBD.

Data Sources, Search Strategy, and Study Selection

We conducted a systematic literature search of multiple databases between March 18, 2018 (date of prior systematic review), and February 28, 2022. The

databases included Ovid Medline, Ovid EMBASE, and Web of Science. Controlled vocabulary supplemented with keywords was used to search for studies reporting the infection risk in patients with IBD. Two authors (V.S. and A.F.) independently reviewed the title and abstract of studies identified in the search to exclude studies that did not answer the research question of interest, based on prespecified inclusion and exclusion criteria. The full text of the remaining articles was reviewed independently to determine whether it contained relevant information. We carried forward relevant studies from prior systematic review. Next, we manually searched the bibliographies of the selected articles, as well as review articles on the topic for additional articles. In addition, we searched clinical trial registries (www.clinicaltrials.gov and www.clinicaltrialsregister.eu), and abstracts from conference proceedings between 2018 and 2022 (Digestive Diseases Week, American College of Gastroenterology annual meeting, and European Crohn's and Colitis Organization annual meeting) for additional studies.

Data Abstraction and Risk of Bias Assessment

After study selection, 2 authors (V.S. and A.F.) independently abstracted data on study and patient characteristics, exposure variables, outcomes, confounding variables, and statistical analyses, using a standardized data abstraction form. The following data were collected from each study: (1) study characteristics: primary author, time period of study including the period of recruitment and follow-up evaluation/year of publication, country of origin, study design (RCT vs cohort studies, clinical registries vs administrative claims-based vs medical record review, prospective vs retrospective), study duration (timing of outcome assessment), and factors pertinent to risk of bias assessment; (2) patient characteristics: age, sex, smoking status, comorbidities, prior infections and/or treatment with antibiotics, disease characteristics (severity, phenotype, duration, and so forth), concomitant medications (corticosteroids, IMM); (3) exposure characteristics: classification of medication exposures, timing of occurrence of event in relation to exposure, and how medication exposures, outcome, and covariates were ascertained; (4) outcomes studied: type and definition of serious infections and incident events; (5) potential confounding variables accounted for in analysis including IBD disease activity (objectively or via surrogates), disease duration, infection risk factors including prior infections, and use of IBD-related and other medications; and (6) statistical approach: unadjusted and adjusted hazard ratio (HR), relative risk, or odds ratio (OR) and 95% CIs, incidence rate of events in each exposure group, and methods to control for bias including use of propensity score methods and inclusion of time-varying covariates.

What You Need to Know

Background

Safety is a key consideration when choosing advanced therapies (biologic agents and oral small-molecule inhibitors/modulators) in patients with inflammatory bowel disease. However, there are limited data on the comparative safety of therapies.

Findings

On meta-analysis of 20 head-to-head studies, compared with tumor necrosis factor α (TNFα) antagonists, vedolizumab was associated with a lower risk of serious infections in patients with ulcerative colitis, but not in patients with Crohn's disease. Ustekinumab is associated with a lower risk of serious infections compared with TNFα antagonists and with vedolizumab in patients with Crohn's disease.

Implications for patient care

Vedolizumab may offer net benefit over TNFα antagonists in patients with ulcerative colitis, but not in Crohn's disease. Ustekinumab may offer net benefit over TNFα antagonists and vedolizumab in patients with Crohn's disease.

Risk of bias for cohort studies was assessed by 2 investigators (V.S. and A.F.) independently, using the Newcastle–Ottawa Scale.[11] In this scale, studies were scored across 3 categories: selection (4 questions), comparability of study groups (1 question), of study groups, and ascertainment of the outcome of interest (3 questions), and all questions had a score of 1. Risk of bias of RCTs was assessed using the Cochrane risk-of-bias tool.

Outcomes Assessed

The primary outcome of interest was risk of serious infections, generally defined as infection requiring hospitalization, need for antibiotics, requiring cessation of immunosuppressive therapy, and/or causing death; in case of RCTs, this was defined based on the Medical Dictionary for Regulatory Activities. Different advanced therapies were compared with each other. Based on available data, key comparisons were vedolizumab vs TNFα antagonists, ustekinumab vs TNFα antagonists, vedolizumab vs ustekinumab, and tofacitinib vs all other advanced therapies. For these comparisons, all TNFα antagonists were grouped together.

To evaluate the stability of the association between different medication exposures and risk of serious infections, and to examine potential sources of heterogeneity, we performed several a priori subgroup analyses for comparisons informed by 3 or more studies, based on the following: IBD phenotype (Crohn's disease [CD] vs

ulcerative colitis [UC]), age (younger vs older patients, >50–65 years at time of biologic initiation), sex (male vs female), prior exposure to biologics, prior serious infections in preceding 1-year baseline, study design (claims-based analysis vs RCTs vs medical record review); and analysis approach (multivariable or propensity score–based analysis vs only univariable analysis). We also performed a sensitivity analysis based on patients on biologic monotherapy or excluding gastrointestinal serious infections (which may be more disease-related rather than treatment-related). We a priori hypothesized that the risk of serious infections may be driven by treatment effectiveness such that vedolizumab may be more effective than TNFα antagonists in patients with UC, but not in patients with CD, and that ustekinumab may be more effective than TNFα antagonists and vedolizumab in patients with CD.

Statistical Analysis

We used the random-effects model described by DerSimonian and Laird[12] to calculate summary OR and 95% CIs. Maximally adjusted risk estimates were used for analysis to account for confounding variables. To estimate what proportion of total variation across studies was owing to heterogeneity rather than chance, an I^2 statistic was calculated.[13] An I^2 value of <30%, 30% to 60%, 60% to 75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively. Between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics (as described earlier). In this analysis, a *P* value for differences between subgroups of less than .05 was considered statistically significant. We also performed univariable meta-regression based on study-level continuous variables when subgroup analysis was not feasible. Publication bias was assessed qualitatively using funnel plots when more than 10 studies were identified for a comparison, and using the Egger regression coefficient.[14] All analyses were performed using Comprehensive Meta-Analysis version 2.0 (Biostat, Inc, Englewood, NJ).

Results

Updating our prior search, an additional 4278 unique studies were identified, of which full text of 24 studies was reviewed in detail. Seventeen published studies were included[2,3,15–29]; in addition, data from 3 unpublished cohorts from the investigator team also were included.[30–32] Hence, data from 20 comparative studies was used for quantitative synthesis (2 RCTs, 18 cohort studies). Of these, 17 cohorts compared the risk of serious infections between vedolizumab vs TNFα antagonists,[2,15,18,19,21–32] 5 cohorts compared ustekinumab vs TNFα antagonists,[2,20,22,30,31] and vedolizumab vs ustekinumab,[16,17,22,30,31] and 1 cohort compared tofacitinib vs TNFα antagonists.[20] We did not identify any comparative study of ozanimod or filgotinib. Supplementary Figure 1 shows the study selection flowsheet.

Table 1 shows the study-level characteristics of included studies. Nine cohort studies were conducted in North America, 7 in Europe, and others were multicenter transcontinental studies. Most studies were designed as retrospective cohort studies, whereas 2 were RCTs and 1 was a prospective cohort study. All studies had a new-user design, implying there was at least a baseline 6- to 12-month time period without receipt of the index biologic; prevalent users were excluded from analysis. Of the cohort studies, 6 studies relied on administrative claims for exposure and outcome ascertainment, and 10 studies relied on medical chart review; 2 cohorts were based on electronic health record–based registry using medication prescriptions and hospitalizations for infections using common data models. Twelve observational studies performed propensity score–based analysis, and 1 reported multivariable analysis; 5 observational studies reported only the unadjusted risk of serious infections with different advanced therapies. The minimum median follow-up evaluation across included studies was 7 months after drug initiation; in 15 studies, the median follow-up evaluation was ≥12 months. The overall risk of serious infections (median, interquartile range [IQR]) in patients with IBD treated with TNFα antagonists, vedolizumab, ustekinumab, and tofacitinib was 6.7 (IQR, 2.7–8.9), 4.2 (IQR, 2.3–7.1), 4.3 (IQR, 3.1–5.6), and 5.6 per 100 patients, respectively.

Table 2 shows the baseline characteristics of patients in each intervention arm in the studies. Four studies were conducted exclusively in older adults. Five studies focused only on patients with CD, and 4 studies focused only on patients with UC. Patient characteristics generally were similar in both treatment arms, particularly in propensity score–matched cohorts. Supplementary Table 1 shows the risk of bias assessment for cohort studies. Overall, these studies were at low–moderate risk of bias. Both RCTs, VARSITY (An Efficacy and Safety Study of Vedolizumab Intravenous [IV] Compared to Adalimumab Subcutaneous [SC] in Participants With Ulcerative Colitis) and SEAVUE (Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year), were rated as low risk of bias.[2,3]

Vedolizumab Vs Tumor Necrosis Factor α Antagonists

On meta-analysis of 17 cohorts of patients with IBD, there was no significant difference in the risk of serious infections between vedolizumab (n = 14,207 patients) vs TNFα antagonists (n = 37,389 patients) (OR, 0.84; 95% CI, 0.68–1.04), with moderate heterogeneity (I^2 = 37%) (Figure 1). On subgroup analysis by disease phenotype, vedolizumab was associated with a 32% lower risk of

Table 1. Characteristics of Included Studies

Study; disease	Geographic location, sites	Study time period, follow-up period, *mo*	Exposure/outcome ascertainment	Comparisons (patients in each group, n)	Definition of serious infections	Patients with infections (in each exposure), n	Analysis approach
Randomized controlled trials							
Sands et al et al,[2] 2019 (VARSITY); UC	Global; multicenter	2015–2019; 12	Case report form	TNF (ADA) (386) vs VDZ (385)	Coded according to MedDRA 21.1	TNF, 8 VDZ, 7	Incidence rates
Irving,[3] 2021 (SEAVUE); CD	Global; multicenter	2018–2021; 12	Case report form	TNF (ADA) (195) vs UST (191)	Coded according to MedDRA 21.1	TNF, 5 UST, 4	Incidence rates
Cohort studies							
Adar et al,[15] 2019; IBD	United States; single center	NR; 12	Medical record review	TNF (131) vs VDZ (105)	Requiring hospitalization, antibiotics, or cessation/ interruption of TIM	TNF, 24 VDZ, 17	Incidence rates; PS adjusted
Alric et al,[16] 2020; CD	France; multicenter	2014–2018; 11	Medical record review	VDZ (132) vs UST (107)	Not defined	VDZ, 14 UST, 6	Incidence rates; PS weighted
Biemans et al,[17] 2020; CD	The Netherlands; multicenter	NR; 12–24	Medical record review	VDZ (128) vs UST (85)	Requiring hospitalization or IV antibiotics/ antiviral medication	VDZ, 3 UST, 5	Incidence rates; PS matched
Bohm et al,[18] 2020; CD	United States, Canada; multicenter	2014–2017; 17	Medical record review	TNF (607) vs VDZ (659)	Requiring hospitalization, antibiotics, or cessation of TIM	TNF, 47 VDZ, 47	Incidence rates; PS weighted
Bressler et al,[19] 2021; IBD	United States, Canada, Greece; multicenter	2014–2017; 24	Medical record review	TNF (497) vs VDZ (598)	NR	TNF, 21 VDZ, 16	Cox PH
Cheng et al,[20] 2022; IBD	United States; multicenter	2008–2019; 7	Administrative claims	UST (2420) vs tofacitinib (305) vs TNF (19096)	Requiring hospitalization	UST, 105 Tofacitinib, 17 TNF, 1407	Cox PH; PS adjusted

Table 1. Continued

Study; disease	Geographic location, sites	Study time period, follow-up period, *mo*	Exposure/outcome ascertainment	Comparisons (patients in each group, n)	Definition of serious infections	Patients with infections (in each exposure), n	Analysis approach
Hupe et al,[21] 2020; UC	France; multicenter	2009–2018; 26	Medical record review	TNF (154) vs VDZ (71)	Requiring hospitalization, antibiotics, or cessation of TIM or death	TNF, 3 VDZ, 0	Cox PH; PS adjusted
Innocenti et al,[22] 2021; IBD	Italy; single center	2013–2019; 24	Medical record review	TNF (447) vs VDZ (85) vs UST (28)	Requiring hospitalization, IV antibiotics, or death	TNF, 12 VDZ, 1 UST, 1	Incidence rates
Kirchgesner et al,[23] 2022; IBD	United States, France; multicenter	2002–2018; 13	Administrative claims	TNF (26,656) vs VDZ (8768)	Requiring hospitalization	TNF, 724 VDZ, 169	Cox PH; PS matched
Kochar et al,[24] 2022; IBD	United States; multicenter	2014–2017; NR	Administrative claims	TNF (1152) vs VDZ (480)	Requiring hospitalization	Incidence rate per 100 person-years: IFX, 5 VDZ, 3	Cox PH; PS-adjusted
Lukin et al,[25] 2022; UC	United States, Canada; multicenter	2014–2017; 11	Medical record review	TNF (268) vs VDZ (454)	Requiring hospitalization, antibiotics, or cessation of TIM or death	TNF, 27 VDZ, 21	Cox PH; PS adjusted
Moens et al,[26] 2021; IBD	Belgium; single center	2015–2019; 12	Medical record review	TNF (99) vs VDZ (96)	Requiring hospitalization or change in TIM	TNF, 2 VDZ, 5	Incidence rates
Pabla et al,[27] 2021; IBD	United States; single center	2005–2019; 15	Medical record review	TNF (104) vs VDZ (108)	Requiring hospitalization or cessation of TIM	TNF, 16 VDZ, 11	Incidence rates
Rundquist et al,[28] 2020; IBD	Sweden; multicenter	2014–2016; 12	Medical record review	TNF (200) vs VDZ (200)	Requiring hospitalization	TNF, 20 VDZ, 13	Cox PH; PS matched
Singh et al,[29] OptumLabs 2022; IBD	United States; multicenter	2014–2018; 14	Administrative claims	TNF (4881) vs VDZ (1106)	Requiring hospitalization	TNF, 435 VDZ, 85	Cox PH; Marginal structural models
Singh et al,[32] Denmark 2022; IBD	Denmark; nationwide	2005–2018; 8	Administrative claims	TNF (377) vs VDZ (377)	Requiring hospitalization	TNF, 24 VDZ, 26	Cox PH; PS matched

Table 1. Continued

Study; disease	Geographic location, sites	Study time period, follow-up period, *mo*	Exposure/outcome ascertainment	Comparisons (patients in each group, n)	Definition of serious infections	Patients with infections (in each exposure), n	Analysis approach
Singh et al,[30] CA-IBD 2022; CD	United States; multicenter	2010–2017; 12	Electronic health record–based registry	TNF (1030) vs VDZ (515) vs UST (221)	Requiring hospitalization	TNF, 71 VDZ, 19 UST, 13 (rates vary in 3 separate PS-matched cohorts)	Cox PH; PS matched
Singh et al,[31] CA-IBD 2022; UC	United States	2010–2017; 12	Electronic health record–based registry	TNF (400) vs VDZ (200) vs UST (64)	Requiring hospitalization	TNF, 31 VDZ, 6 UST, 2 (rates vary in 3 separate PS-matched cohorts)	Cox PH; PS matched

ADA, adalimumab; CA-IBD, California IBD cohort; CD, Crohn's disease; MedDRA, Medical Dictionary for Regulatory Activities; IFX, infliximab; IV, intravenous; NR, not reported; PH, proportional hazard; PS, propensity score; SEAVUE, Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year; TIM, targeted immune modulator; TNF, tumor necrosis factor α antagonists; UC, ulcerative colitis; UST, ustekinumab; VDZ, vedolizumab.

serious infections compared with TNFα antagonists in patients with UC (11 cohorts; OR, 0.68; 95% CI, 0.56–0.83) with minimal heterogeneity ($I^2 = 0\%$), but not in patients with CD (9 cohorts; OR, 1.03; 95% CI, 0.78–1.35) with moderate heterogeneity ($I^2 = 42\%$) (P value for difference in subgroups = .02) (Figure 2).

There was no significant difference in the risk of serious infections between vedolizumab vs TNFα antagonists in older adults (6 cohorts; OR, 0.81; 95% CI, 0.56–1.16; $I^2 = 0\%$). When limiting the analysis to patients treated with biologic monotherapy, no differences were observed in the risk of serious infections (3 cohorts; OR, 0.75; 95% CI, 0.44–1.30). Similarly, when excluding serious infections of gastrointestinal origin (which may presumptively be disease-related), no significant differences were observed between vedolizumab vs TNFα antagonists (3 cohorts; OR, 0.68; 95% CI, 0.43–1.07). Overall findings were stable on subgroup analysis by age, sex, prior TNFα antagonist exposure, prior serious infections, or approach to analysis (Table 3). On meta-regression, disease duration ($P = .25$), concomitant IMM ($P = .30$), and concomitant corticosteroid use ($P = .58$) did not influence the association. We did not observe any evidence of publication bias (Egger regression coefficient, $P = .21$).

Ustekinumab Vs Tumor Necrosis Factor α Antagonists

On meta-analysis of 5 cohorts, there was no significant difference in the risk of serious infections between ustekinumab (n = 2924 patients) vs TNFα antagonists (n = 20,308) (OR, 0.63; 95% CI, 0.38–1.05) with moderate heterogeneity ($I^2 = 50\%$) (Figure 3). On subgroup analysis by disease phenotype, ustekinumab was associated with a 51% lower risk of serious infections compared with TNFα antagonists in patients with CD (3 cohorts; OR, 0.49; 95% CI, 0.25–0.93) with minimal heterogeneity ($I^2 = 16\%$). In 1 study using the Medicare database, although results were not stratified by disease phenotype, 85% of patients treated with ustekinumab had CD. In this study, ustekinumab was associated with a lower risk of all infections compared with TNFα antagonists (HR, 0.93; 95% CI, 0.86–0.99), with a similar trend when limited to serious infections (HR, 0.84; 95% CI, 0.66–1.03). A single study reported no significant difference in the risk of serious infections between ustekinumab vs TNFα antagonists in patients with UC, although in this study ustekinumab was used off-label before regulatory approval for UC (HR, 0.44; 95% CI, 0.09–2.08). The number of studies was limited and did not provide sufficient data for additional subgroup analysis or meta-regression.

Vedolizumab Vs Ustekinumab

On meta-analysis of 5 cohorts, there was no significant difference in the risk of serious infections between

Table 2. Characteristics of Patients Participating in the Included Studies

Study	Exposure	Patients, n	Age, *y*, mean ± SD, or median (range)	Females, %	CD, %	Disease duration, mean, SD	Concomitant steroids, %	Concomitant IMM, %	Prior biologic exposure, %	DM/COPD, %
Sands et al,[2] 2019 (VARSITY)	TNF	385	41 ± 13	44	0	6.4 ± 6.0	36	26	21	NR
	VDZ	383	41 ± 14	39	0	7.3 ± 7.2	36	26	21	NR
Irving et al,[3] 2021 (SEAVUE)	TNF	195	NR	NR	100	2.6	NR	NR	NR	NR
	UST	191	NR	NR	100	2.6	NR	NR	NR	NR
Adar et al,[15] 2019	TNF	131	68 ± 6	42	52	13 ± 15	60	21	14	NR
	VDZ	103	68 ± 6	42	50	16 ± 14	70	23	60	NR
Alric et al,[16] 2020	VDZ	132	40 ± 15	55	100	12.2 (6.2–16.7)	49	42	72	NR
	UST	107	40 ± 15	51	100	10.7 (6.4–18.9)	28	23	54	NR
Biemans et al,[17] 2021	VDZ	128	37 (27–51)	66	100	11.0 (6.4–18.1)	31	19	100	NR
	UST	85	39 (29–52)	60	100	15.3 (8.4–21.9)	12	24	100	NR
Bohm et al,[18] 2020	TNF	607	36 ± 15	47	100	3–6	27	46	52	NR
	VDZ	659	40 ± 15	58	100	12 ± 13	46	41	91	NR
Bressler et al,[19] 2022	TNF	497	CD, 40 ± 15 UC, 40 ± 16	CD, 49 UC, 51	55	≥5 y, % CD, 36 UC, 29	CD, 13 UC, 35	NR	NR	NR
	VDZ	598	CD, 52 ± 17 UC, 46 ± 17	CD, 48 UC, 41	36	≥5 y, % CD, 53 UC, 51	CD, 15 UC, 31	NR	NR	NR
Cheng et al,[20] 2022	TNF	19096	39 ± 17	51	61	1.9 ± 2.1	NR	NR	1	NR
	UST	2420	42 ± 15	57	86	2.7 ± 2.8	NR	NR	30	NR
	Tofacitinib	305	44 ± 16	56	18	2.8 ± 2.7	NR	NR	36	NR
Hupe et al,[21] 2020	TNF	154	43 ± 17	36	0	6.4 ± 7.4	49	58	NR	NR
	VDZ	71	43 ± 17.3	52	0	9.1 ± 8.7	44	16	NR	NR
Innocenti et al,[22] 2021	TNF	447	28 (21–41)	47	60	≥10 y, %: 62%	NR	23	63	NR
	VDZ	85	43 (27–57)	37	45	≥10 y, %: 63%	NR	18	77	NR
	UST	28	27 (19–35)	54	100	≥10 y, %: 75%	NR	7	96	NR
Kirchgesner et al,[23] 2022	TNF	26,656	TNF-exposed, 41 ± 14; 41 ± 15; 41 ± 14 TNF-naive, 43 ± 15; 47 ± 17	TNF-exposed, 54; TNF-naive, 51	53	NR	NR	NR	44	8/17
	VDZ	8768	TNF-exposed, 41 ± 14; 43 ± 16; 41 ± 15 TNF-naïve, 43 ± 15; 48 ± 18	TNF-exposed, 53; TNF-naïve, 51	52	NR	NR	NR	50	8/18

Table 2. Continued

Study	Exposure	Patients, n	Age, *y*, mean ± SD, or median (range)	Females, %	CD, %	Disease duration, mean, SD	Concomitant steroids, %	Concomitant IMM, %	Prior biologic exposure, %	DM/COPD, %
Kochar et al,[24] 2022	TNF	1152	71 (68–76)	59	54	NR	38	18	NR	NR
	VDZ	480	71 (68–76)	55	57	NR	30	16	NR	NR
Lukin et al,[25] 2022	TNF	268	38 ± 16	53	0	3–6 (6–11)	54	43	39	NR
	VDZ	454	42 ± 17	50	0	6 ± 11	54	33	69	NR
Moens et al,[26] 2021	TNF	99	CD, 31 (24–47); UC, 36 (28–48)	CD, 53 UC, 52	55	CD, 3 (0–17); UC, 4 (1–8)	CD, 17 UC, 13	CD, 11 UC, 15	NR	NR
	VDZ	96	CD, 43 (27–57); UC, 41 (28–56)	CD, 48 UC, 60	34	CD, 4 (1–11); UC, 5 (1–11)	CD, 21 UC, 19	CD, 6 UC, 6	NR	NR
Pabla et al,[27] 2021	TNF	104	66 (63–70)	53	67	10 (2–25)	NR	NR	NR	NR
	VDZ	108	68 (64–72)	48	57	16 (5–30)	NR	NR	NR	NR
Rundquist et al,[28] 2020	TNF	200	CD, 42 (27–55); UC, 34 (26–44)	CD, 50 UC, 39	50	CD, 10 (3–18); UC, 7 (3–14)	CD, 50 UC, 48	CD, 17 UC, 30	NR	NR
	VDZ	200	CD, 45 (32–54); UC, 35 (25–48)	CD, 47 UC, 37	50	CD, 10 (422); UC, 6 (212)	CD, 40 UC, 52	CD, 20 UC, 30	NR	NR
Singh et al,[29] OptumLabs 2022	TNF	4881	41 ± 15	48	60	NR	NR	NR	NR	9/13
	VDZ	1106	44 ± 16	52	39	NR	NR	NR	NR	13/13
Singh et al,[31] Denmark 2022	TNF	377	>50 y = 100%	55	48	NR	21	13	71	NR
	VDZ	377	>50 y = 100%	54	47	NR	32	7	71	NR
Singh et al,[30] CA-IBD, 2022	TNF	1030	44 ± 16	55	100	NR	34	25	23	NR
	UST	515	42 ± 16	54	100	NR	34	27	44	NR
	VDZ	221	41 ± 19	57	100	NR	46	25	38	NR
Singh et al,[31] CA-IBD, 2022	TNF	400	40 ± 16	50	0	NR	34	25	22	NR
	VDZ	200	41 ± 19	48	0	NR	32	24	35	NR
	UST	64	42 ± 17	50	0	NR	33	31	42	NR

CA-IBD, California IBD cohort; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IMM, immunomodulator; NR, not reported; SEAVUE, Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year; TNF, tumor necrosis factor α antagonists; UC, ulcerative colitis; UST, ustekinumab; VARSITY, An Efficacy and Safety Study of Vedolizumab Intravenous [IV] Compared to Adalimumab Subcutaneous [SC] in Participants With Ulcerative Colitis; VDZ, vedolizumab.

vedolizumab (n = 694 patients) vs ustekinumab (n = 726 patients) (OR, 1.96; 95% CI, 0.92–1.14) with moderate heterogeneity (I^2 = 50%) (Supplementary Figure 2). On subgroup analysis by disease phenotype, vedolizumab was associated with a 2.5 times higher risk of serious infections compared with ustekinumab in patients with CD (3 cohorts; OR, 2.50; 95% CI, 1.07–5.83) with considerable heterogeneity (I^2 = 67%). A single study reported no significant difference in the risk of serious infections between vedolizumab vs ustekinumab in patients with UC, although in this study ustekinumab was used off-label before regulatory approval for UC (HR, 1.00; 95% CI, 0.18–5.55). The number of studies was limited and did not provide sufficient data for additional subgroup analysis or meta-regression.

Other Advanced Therapies

We identified only 1 study comparing the risk of serious infections between tofacitinib vs TNFα antagonists. In this study, using a US health insurance database, Cheng et al[20] compared 305 patients with IBD treated with tofacitinib vs 19,096 patients treated with TNFα antagonists. Using Cox proportional hazard analysis, there was no significant difference in the risk of all infections (HR, 0.97; 95% CI, 0.75–1.24) or serious infections (HR, 0.59; 95% CI, 0.27–1.05) between tofacitinib vs TNFα antagonists. We did not identify any comparative studies of ozanimod or filgotinib.

Discussion

Treatment safety is a key consideration when choosing advanced therapies for the management of patients with IBD. In this systematic review and meta-analysis of 20 head-to-head real-world studies including >55,000 patients treated with advanced therapies, we made several key observations on the comparative risk of serious infections with different classes of advanced therapies. First, we observed that overall there was no significant differences in the risk of serious infections with vedolizumab vs TNFα antagonists. However, in a subset of patients with UC, vedolizumab was associated with a 32% lower risk of serious infections compared with TNFα antagonists and may offer net benefit. No difference was observed in the risk of serious infections between the 2 agents in patients with CD. This association was not influenced by age, prior biologic exposure, disease duration, or concomitant use of IMMs. Second, we observed that ustekinumab may be associated with a lower risk of serious infections compared with TNFα antagonists, and compared with vedolizumab, in patients with CD. There was a paucity of data on the comparative safety of ustekinumab, tofacitinib, filgotinib, and ozanimod in UC, which is a key knowledge gap. Overall, these data suggest that different advanced therapies have differing safety profiles, which is not entirely driven by the drug's purported intrinsic immune suppression and may be influenced significantly by IBD phenotype (and the drug's effectiveness in controlling IBD). Combining this evidence on comparative safety of advanced therapies with knowledge on the comparative effectiveness of different therapies from head-to-head trials and network meta-analyses can help inform net-benefit assessment and promote shared decision making for clinical practice.

Two key factors determine the safety of immunosuppressive therapies in patients with IBD.[33] First, the intrinsic systemic immune suppression potential of the agent, and, second, its effectiveness in controlling disease, achieving corticosteroid-free remission, and avoiding disease-related complications. Vedolizumab's gut specificity was confirmed in a vaccination study in healthy volunteers, in which it selectively reduced response to orally administered antigens, but not to parenterally administered antigens.[34] Exposure to vedolizumab also does not seem to attenuate response to the coronavirus disease vaccine.[35] This suggests that vedolizumab is less systemically immunosuppressive compared with TNFα antagonists. Data from RCTs and network meta-analyses suggest that vedolizumab may be as effective as infliximab, and more effective than adalimumab, in patients with moderate to severe UC.[2,4,9] Hence, the high efficacy of vedolizumab in achieving and maintaining remission, combined with a lower degree of immunosuppression, may explain why vedolizumab was associated with a lower risk of serious infections than TNFα antagonists in patients with UC. Consequently, vedolizumab may offer net benefit in patients with UC. In contrast, vedolizumab may be less effective than TNFα antagonists in patients with CD, particularly in biologic-exposed patients, and in patients with high-risk phenotype such as perianal disease and high inflammatory burden.[5,8] As a result, despite a lower degree of direct systemic immunosuppression with vedolizumab, there was no safety advantage with vedolizumab vs TNFα antagonists in patients with CD. Patients with CD with inadequate disease control may be more prone to disease-related complications including serious infections such as intra-abdominal and perianal abscesses. In a claims-based study, we previously observed that risk of serious infections of gastrointestinal origin in patients with CD was 2.9 times with vedolizumab compared with TNFα antagonists.[29] In addition, inadequate disease control may lead to a higher burden of corticosteroid use and poor functional status and frailty predisposing to extraintestinal serious infections. In our analysis, even after excluding gastrointestinal serious infections, we did not observe any significant differences in the risk of serious infections between vedolizumab and TNFα antagonists. From a patient's perspective, the safety and effectiveness of a treatment strategy may be more valuable than the absolute immune suppression potential of a specific agent. Hence, vedolizumab may not offer a net benefit over

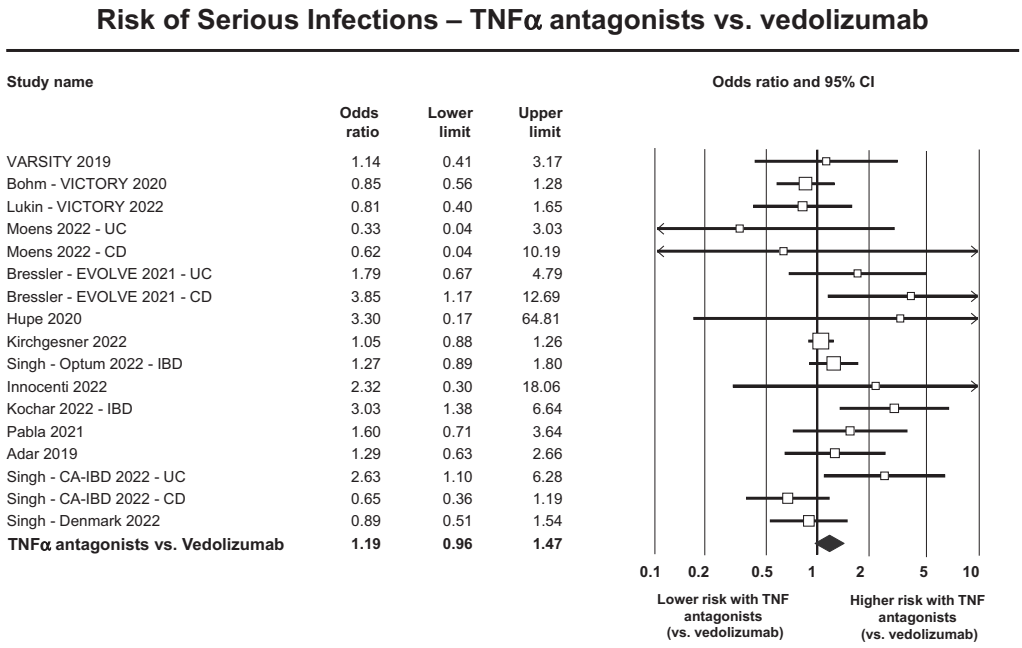

Figure 1. Risk of serious infections with tumor necrosis factor α (TNFα) antagonists vs vedolizumab in all patients with inflammatory bowel disease (IBD). In a meta-analysis of 17 cohorts of patients with IBD, there was no significant difference in the risk of serious infections between vedolizumab (n = 14,207 patients) vs TNFα antagonists (n = 37,389 patients) (odds ratio, 0.84; 95% CI, 0.68–1.04), with moderate heterogeneity (I^2 = 37%). CA-IBD, California IBD cohort; CD, Crohn's disease; UC, ulcerative colitis.

TNFα antagonists in patients with CD. In a registry-based study in patients with rheumatoid arthritis, Strangfeld et al[36] observed that effective disease control and a decrease in corticosteroid use with TNFα antagonists was associated with progressive decrease in the risk of serious infections over time, relative to conventional disease-modifying antirheumatic drugs; this treatment effect explained a 32% relative decrease in risk of serious infections with TNFα antagonists vs disease-modifying antirheumatic drugs, from year 1 to year 2. Unfortunately, this concept of treatment effect could not be readily examined in this systematic review. Most studies adjusted for concomitant exposure to corticosteroids at baseline, but only a few studies adjusted for baseline disease activity. Critically, none of the studies accounted simultaneously for time-varying treatment effectiveness and on-treatment evolution of risk of serious infections.

We observed that the risk of serious infections was lower in patients with CD treated with ustekinumab vs TNFα antagonists. Ustekinumab and TNFα antagonists have comparable efficacy in patients with moderate to severe CD, based on the recent SEAVUE trial and network meta-analysis.[3,5,8] This may explain why ustekinumab, which may not have as profound an immunosuppressive effect as TNFα antagonists based on vaccine-response studies, may be associated with a lower risk of serious infections in patients with CD.[37] Similar observations have been observed in psoriasis. In the US Psoriasis Longitudinal Assessment and Registry with 11,466

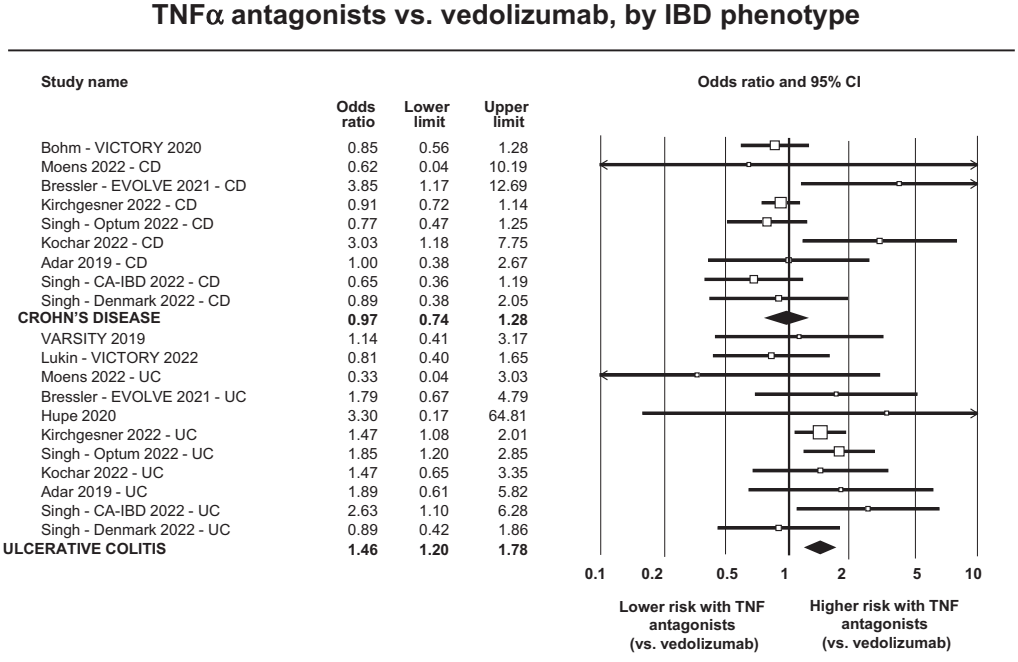

Figure 2. Risk of serious infections with tumor necrosis factor α (TNFα) antagonists vs vedolizumab in patients with Crohn's disease (CD) and ulcerative colitis (UC). Vedolizumab was associated with a 32% lower risk of serious infections compared with TNFα antagonists in patients with UC (11 cohorts; odds ratio, 0.68; 95% CI, 0.56–0.83) with minimal heterogeneity (I^2 = 0%), but not in patients with CD (9 cohorts; odds ratio, 1.03; 95% CI, 0.78–1.35) with moderate heterogeneity (I^2 = 42%) (*P* value for difference in subgroups = .02). CA-IBD, California IBD cohort.

Table 3. Subgroup Analysis Comparing the Risk of Serious Infections With Vedolizumab Vs TNFα Antagonists

Risk of serious infections	Cohorts, n	Odds ratio (95% CI) (vedolizumab vs TNFα antagonists)	I^2	*P* value for difference in subgroups
IBD subtype				.02
Crohn's disease		1.03 (0.78–1.35)	42%	
Ulcerative colitis		0.68 (0.56–0.83)	0%	
Age				.93
Younger		0.83 (0.68–1.00)	52%	
Older		0.81 (0.56–1.16)	0%	
Sex				.56
Male		1.11 (0.89–1.37)	0%	
Female		1.01 (0.80–1.27)	0%	
Prior TNF exposure				.51
TNF naïve		0.89 (0.44–1.82)	54%	
TNF exposed		1.19 (0.75–1.89)	54%	
Prior serious infections				.83
Yes		0.85 (0.56–1.28)	–	
No		0.89 (0.74–1.08)	0%	
Analysis approach				.75
Adjusted (PS, MV or RCT)	13	0.84 (0.67–1.05)	47%	
Unadjusted	4	0.74 (0.37–1.49)	0%	

CI, confidence interval; IBD, inflammatory bowel disease; MV, multivariable; PS, propensity score; RCT, randomized controlled trial; TNFα, tumor necrosis factor α.

patients, the absolute risk of serious infections with ustekinumab (0.83 per 100 person-years) was lower compared with infliximab (2.49 per 100 person-years).[38] Network meta-analyses and observational studies also have suggested that ustekinumab may be more effective than vedolizumab in patients with moderate to severe CD, particularly those with prior failure of TNFα antagonists.[5,39] This, combined with the likely comparable systemic immune suppression potential of both ustekinumab and vedolizumab, may explain the lower risk of serious infections with ustekinumab vs vedolizumab in patients with CD.

There were several strengths of this systematic review including the following: (1) direct comparative assessment of risk of serious infections with different classes of advanced therapies; (2) minimal heterogeneity across all analyses, through well-defined inclusion and exclusion criteria; (3) multiple subgroup analyses confirmed the stability and consistency of findings, particularly for the comparison between vedolizumab and TNFα antagonists; and (4) inclusion of conference proceedings and unpublished literature. However, there were several limitations that should be acknowledged. First, the meta-analysis relied primarily on observational studies. Observational studies lack the experimental random allocation of the intervention necessary to test exposure–outcome hypotheses optimally. Despite statistical approaches to adjusting for several covariates, it is

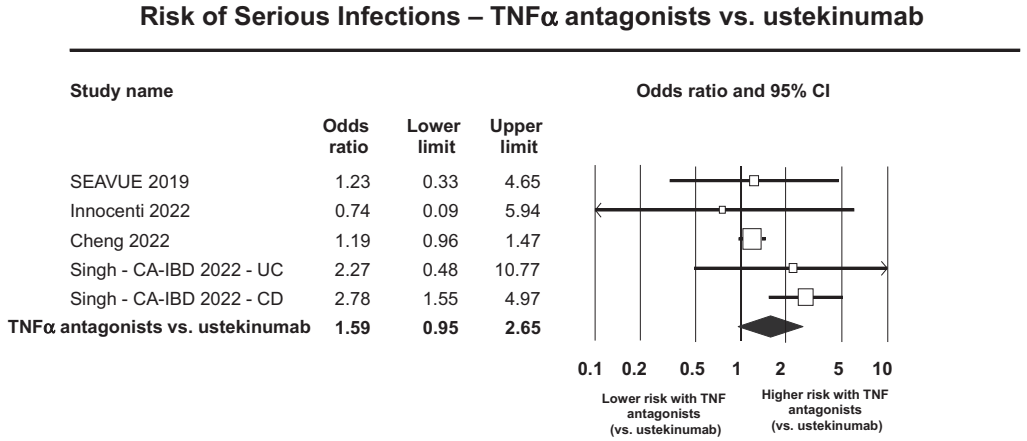

Figure 3. Risk of serious infections with tumor necrosis factor α (TNFα) antagonists vs ustekinumab in all patients with inflammatory bowel disease. In a meta-analysis of 5 cohorts, there was no significant difference in the risk of serious infections between ustekinumab (n = 2924 patients) vs TNFα antagonists (n = 20,308) (odds ratio, 0.63; 95% CI, 0.38–1.05) with moderate heterogeneity (I^2 = 50%). CA-IBD, California IBD cohort; CD, Crohn's disease; SEAVUE, Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year; UC, ulcerative colitis.

not possible to eliminate the potential of residual confounding or selection bias. However, head-to-head clinical trials are few, highly selective, and are underpowered for safety end points such as serious infections, and, hence, providers need to rely on observational studies. Second, there were subtle differences in the definition of exposures and outcomes, depending on the data source. The definition of serious infections was not standardized in real-world studies, with no adjudication of outcomes, different provider thresholds for hospitalization, and use of antibiotics in different jurisdictions. Six studies incorporated any use of antibiotics in defining serious infections, of which only 2 studies focused only on intravenous antibiotics; use of oral antibiotics may not represent truly serious infections because providers may have a low threshold to prescribe antibiotics in patients on immunosuppressives. In several studies, on-treatment, time-varying exposure to corticosteroids was not well characterized. However, as noted earlier, there was low heterogeneity across most analyses, and results were stable on multiple subgroup analyses, including analytic approach. Third, there were several differences between studies that we could not account for adequately, such as duration of IBD, objective assessment of disease behavior and activity, concomitant medications, including dose of corticosteroids and use of narcotics. Fourth, there was a paucity of comparative safety studies of ustekinumab, tofacitinib, figotinib, and ozanimod. Fifth, we focused on serious infections as a marker of treatment safety; other safety outcomes such as risk of malignancy, major adverse cardiovascular outcomes, and venous thromboembolism also are important to consider in shared decision making.

In conclusion, based on a systematic review and meta-analysis of 20 comparative studies, we observed differences in the risk of serious infections with different advanced immunosuppressive therapies. Overall, no differences were observed in the risk of serious infections between vedolizumab and TNFα antagonists, particularly in patients with CD; in patients with UC, vedolizumab was safer and may offer net benefit. In patients with CD, ustekinumab may be associated with a lower risk of serious infections compared with TNFα antagonists and vedolizumab, and may offer net benefit. As treatment options for management of IBD expand with availability of several newer non–TNF-targeting biologics and oral small-molecule inhibitors/modulators, well-designed comparative real-world studies are warranted to optimally inform risks associated with these agents, especially over longer-term horizons, which are not captured in clinical trials.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.07.032.

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Siddharth Singh, MD (Conceptualization: Lead; Data curation: Equal; Formal analysis: Lead; Funding acquisition: Lead; Supervision: Lead; Writing – original draft: Lead)

Conflicts of interest
These authors disclose the following: Christopher Ma has received consulting fees from AbbVie, Alimentiv, Amgen, AVIR Pharma, Inc, BioJAMP, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Janssen, McKesson, Mylan, Takeda, Pendopharm, Pfizer, and Roche, speaker's fees from AbbVie, Amgen, AVIR Pharma, Inc, Alimentiv, Ferring, Janssen, Takeda, and Pfizer, and research support from Ferring and Pfizer; Cesare Hassan has received consulting fees and equipment on loan from Medtronic and Fujifilm, and has received consulting fees from Pentax; Alessandro Repici has received consulting fees and research grants from Fujifilm, has served on the advisory board for Medtronic, has received speaker fees from Medtronic and Boston Scientific, has received research grants from Boston Scientific, and has received consulting fees from Cosmo Pharmaceuticals; Vipul Jairath has

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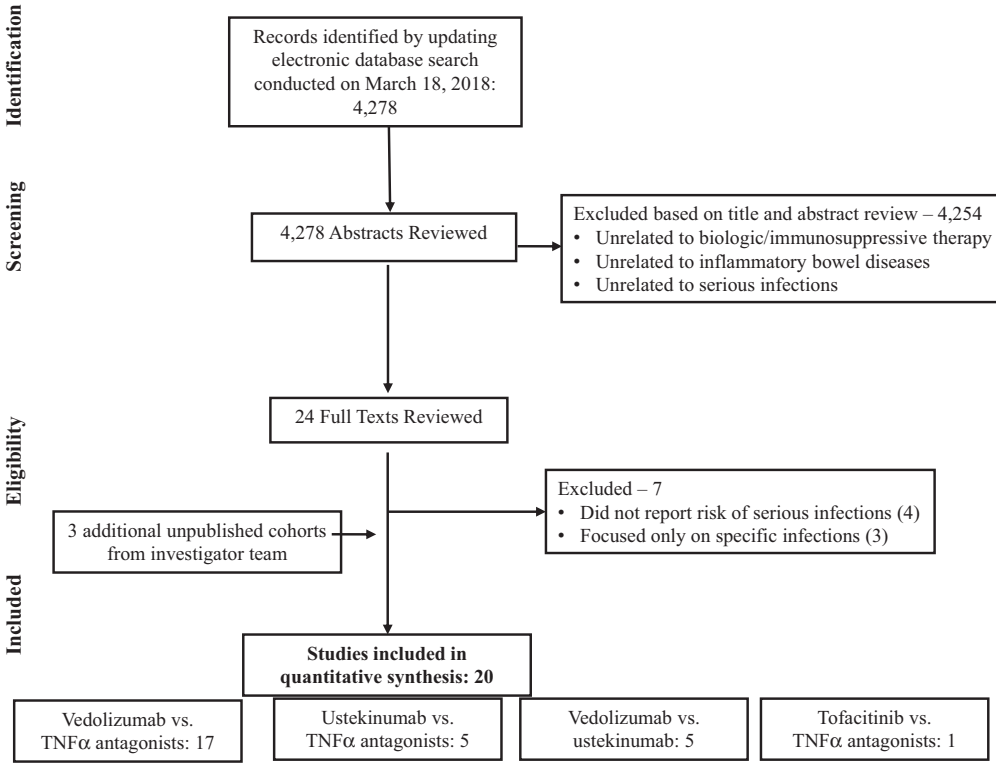
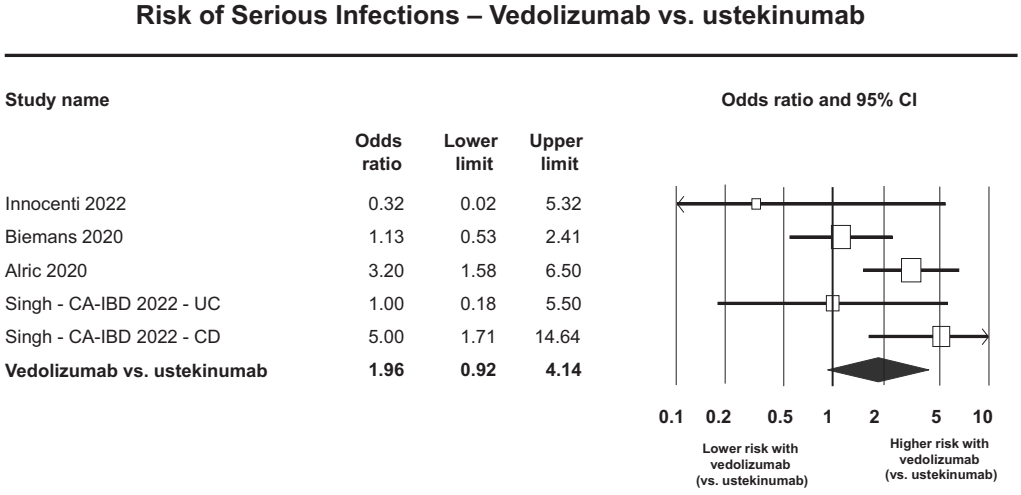


Supplementary Figure 1. Study selection flowsheet. TNFα, tumor necrosis factor α.



Supplementary Figure 2.
Risk of serious infections with vedolizumab vs ustekinumab in all patients with inflammatory bowel disease. In a meta-analysis of 5 cohorts, there was no significant difference in the risk of serious infections between vedolizumab (n = 694 patients) vs ustekinumab (n = 726 patients) (odds ratio, 1.96; 95% CI, 0.92–1.14) with moderate heterogeneity (I^2 = 50%). CA-IBD, California IBD cohort; CD, Crohn's disease; UC, ulcerative colitis.

Supplementary Table 1. Risk of Bias of Cohort Studies Included in the Systematic Review According to the Newcastle–Ottawa Scale

	Selection				Outcome			Comparability	
Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Score
Adar[15]	★	★	★	★	★	★	★	★	8
Alric[16]	★	★	★	★	–	★	★	–	6
Bohm[18]	★	★	★	★	★	★	★	★	8
Hupe[21]	★	★	★	★	★	★	★	★	8
Rundquist[28]	★	★	–	★	★	★	★	★	7
Biemans[17]	★	★	★	★	★	★	★	★	8
Moens[26]	★	★	★	★	★	★	★	–	7
Bressler[19]	★	★	★	★	★	★	★	★	8
Innocenti[22]	★	★	★	★	★	★	★	–	7
Kochar[24]	★	★	★	★	★	★	★	★	8
Pabla[27]	★	★	★	★	★	★	★	–	7
Lukin[25]	★	★	★	★	★	★	★	★	8
Kirchgesner[23]	★	★	★	★	★	★	★	★	8
Singh–OptumLabs[29]	★	★	★	★	★	★	★	★	8
Cheng[20]	★	★	★	★	★	★	★	★	8
Singh - Denmark[32]	★	★	★	★	★	★	★	★	8
Singh – CA-IBD - CD[30]	★	★	–	★	★	★	★	★	8
Singh – CA-IBD - UC[31]	★	★		★	★	★	★	★	8

NOTE. Risk of bias of randomized trials was assessed using the Cochrane risk-of-bias tool, and both trials (VARSITY [An Efficacy and Safety Study of Vedolizumab Intravenous [IV] Compared to Adalimumab Subcutaneous [SC] in Participants With Ulcerative Colitis] and SEAVUE [Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year]) were rated as low risk of bias. Items were as follows: 1, representativeness of the exposed cohort; 2, selection of the nonexposed cohort; 3, ascertainment of exposure; 4, demonstration that outcome of interest was not present at the start of the study; 5, assessment of outcome; 6, follow-up period was long enough for outcomes to occur; 7, adequacy of follow-up evaluation (>75% follow-up evaluation, or description for those lost); and 8, comparability of cohorts on the basis of the design or analysis.
CA-IBD, California IBD cohort.