Decreased risk of treatment failure with vedolizumab and thiopurines combined compared with vedolizumab monotherapy in Crohn's disease.

Julien Kirchgesner, Rishi Desai, Maria Schneeweiss, Laurent Beaugerie, Sebastian Schneeweiss, Seoyoung Kim

Decreased risk of treatment failure with vedolizumab and thiopurines combined compared to vedolizumab monotherapy in Crohn's disease

Julien Kirchgesner, MD, PhD [1,2], Rishi J. Desai, PhD [1], Maria C. Schneeweiss, MD [1], Laurent Beaugerie, MD, PhD [2], Sebastian Schneeweiss, MD, ScD [1], Seoyoung C. Kim, MD, ScD [1,3]

(1) Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

(2) Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Saint-Antoine, Department of Gastroenterology, Paris, France

(3) Division of Rheumatology, Inflammation, and Immunity, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Corresponding author:

Julien Kirchgesner

Division of Pharmacoepidemiology and Pharmacoeconomics,

Department of Medicine, Brigham and Women's Hospital and Harvard Medical School

1620 Tremont Street, Suite 3030, Boston, MA 02120

Phone: 617-278-0930

Fax: 617-232-8602

E-mail: julien.kirchgesner@gmx.com

Body text word count: 3999

Abstract

Objective: While infliximab combined to thiopurines is more effective than infliximab monotherapy in patients with Crohn's disease (CD) and ulcerative colitis (UC), the impact of adding thiopurines to vedolizumab remains controversial. We emulated two target trials comparing the effectiveness of combination therapy versus vedolizumab monotherapy in CD and UC.

Design: Based on two U.S. and the French nationwide healthcare databases, patients with CD and UC who initiated vedolizumab were identified. The study methodology, including confounding adjustment and outcome definitions, were previously validated in successful emulations of the SONIC and SUCCESS trials. Risk ratios for treatment failure based on hospitalisation or surgery related to disease activity, treatment switch, or prolonged corticosteroids use, were estimated after 1:1 propensity score (PS) matching.

Results: Among a total of 10,299 vedolizumab users, 804 CD and 1,088 UC pairs of combination therapy versus vedolizumab monotherapy users were PS-matched. Treatment failure occurred at week 26 in 236 (29.3%) and 376 (34.3%) CD patients and at week 16 in 236 (21.7%) and 263 (24.2%) UC patients initiating combination therapy and vedolizumab monotherapy, respectively. The risk of treatment failure was decreased with combination therapy compared to vedolizumab monotherapy in CD (RR 0.85, 95%CI 0.74 to 0.98), and to a lesser extent in UC (RR 0.90, 0.77 to 1.05). Findings were consistent across databases.

Conclusion: Using validated methodologies, combination therapy with vedolizumab and thiopurines was associated with lower treatment failure compared to vedolizumab monotherapy in CD but not UC across the US and France.

What is already known on this topic?

Infliximab combined with thiopurines is more effective than infliximab monotherapy in inflammatory bowel disease (IBD), but the impact of adding thiopurines to vedolizumab remains controversial. No clinical trials are currently performed to address this question.

What this study adds?

Based on two emulated pragmatic clinical trials and using a large two-nation population-based cohort of patients with Crohn's disease and ulcerative colitis, we observed that combination therapy with vedolizumab and thiopurines was associated with lower treatment failure compared to vedolizumab monotherapy in patients with Crohn's disease but not ulcerative colitis.

How this study might affect research, practice or policy?

The present study is the first population-based study to provide head-to-head comparisons of vedolizumab and thiopurines combined versus vedolizumab monotherapy. These findings may help to guide treatment decisions in patients with IBD requiring vedolizumab.

Introduction

Vedolizumab is the first biologic agent approved for the treatment of both inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), after the era of tumor necrosis factor antagonists (anti-TNF).[1,2] While the combination of infliximab and thiopurines is more effective than monotherapy with either of these drugs in patients with IBD, [3,4] the impact of adding thiopurines with vedolizumab remains controversial. A meta-analysis including 2,053 patients with CD and 1,260 patients with UC treated with vedolizumab, among whom 933 patients were treated with the combination of vedolizumab and either thiopurines or methotrexate, reported no benefit of concomitant immunosuppressive therapy on clinical benefit in either CD or UC.[5] In addition to the heterogeneous definition of clinical benefit across studies included, none of these studies were aimed to address this question and no adjustment for disease severity was possible, which limits the validity of the results. A recent study including 131 patients with IBD treated with the combination of vedolizumab and either thiopurines or methotrexate reported no differences in clinical response between combination therapy and vedolizumab monotherapy in the overall cohort of patients with IBD, but the effect differed according to IBD subtype, suggesting potential incremental effectiveness by adding a co-immunosuppressant with vedolizumab in CD but not UC.[6]

Ideally, this question would be addressed by a randomized controlled trial (RCT), but no dedicated RCTs are planned,[7] and it is unlikely that we will have RCT evidence any time soon. In the absence of RCT evidence, real-world evidence (RWE) derived from real-world data (RWD) can provide valuable information on treatment effectiveness based on the head-to-head comparison.[8] We recently successfully conducted an RWD cohort study in the US and French claims databases and replicated the findings of the SONIC and SUCCESS trials for the effectiveness of infliximab and thiopurines compared to infliximab monotherapy by emulating the RCTs as closely as possible.[9,10] This highlights the opportunities of principled RWE analysis by emulating RCT designs to study treatment effectiveness in patients with IBD in clinical practice when corresponding RCT data are lacking.[11,12]

We aimed to emulate two target trials studying the effectiveness of combination therapy with vedolizumab and thiopurines compared to vedolizumab monotherapy in CD and UC.

Methods

Data source

This study was conducted by using two U.S. health care claims databases, IBM MarketScan (MarketScan) 2009-2018 and Optum's de-identified Clinformatics® Data Mart Database (Optum) 2009-2020, and the French administrative health database 2009-2018 (*Système National des Données de Santé*, SNDS). Patients enrolled in the MarketScan and Optum databases are representative of a commercially insured population in the U.S.; the SNDS insures 95% of the French population. The two U.S. databases are de-identified and contain demographic data and longitudinal information on all encounters with the professional healthcare system while subjects are enrolled in the health plan, including hospitalisation, outpatient visits, procedures, and pharmacy dispensing. Similarly, the SNDS contains data on all drug reimbursements, inpatient and outpatient medical care prescribed or provided by healthcare professionals.[13] The SNDS also includes the patient's status with respect to full reimbursement of care for long-term diseases (LTDs), which includes IBD and allows to assess the date of IBD diagnosis.[14] The study was approved by the institutional review board of the Brigham and Women's Hospital, and the French Data Protection Authority.

Design and study population

This observational study emulated two pragmatic clinical trials comparing the effectiveness of vedolizumab and thiopurines combined compared to vedolizumab monotherapy in patients with CD and UC, and it generally follows the approach used in the SONIC and SUCCESS trials.[3,4] Variables assessed in clinical trials studying drugs for the treatment of IBD may not be included in RWD, notably clinical scores usually considered as effectiveness outcomes. The emulation of RCTs by RWE studies may help to calibrate an effectiveness outcome measurable in RWD, that could be applied to other treatment comparisons within the same indication. Thus, we first developed an effectiveness outcome measure and a methodological approach for confounding adjustment, which allowed us to successfully replicate findings of the SONIC and the SUCCESS trials using the same databases included in this study.[9,10] The same data and analytic framework was applied in this study. Supplementary table 1 outlines the protocol of such a trial and the emulation procedure.

We identified adults (≥18 years) with at least one visit for CD and UC using the International Classification of Diseases 9th (ICD-9) or 10th (ICD-10) Revision codes for CD and UC. In the SNDS database, CD and UC diagnoses were based on previously published algorithms,[14–16], and the date of CD or UC diagnosis was defined as the earliest diagnosis date either from hospital discharge diagnosis or from LTD diagnosis. Patients included in MarketScan and

Optum databases were required to have continuous enrolment during the baseline period of 180 days before initiation of vedolizumab. Patients with CD and UC were separately assessed. Some patients may have diagnosis codes for both CD and UC during the baseline period. While these patients are usually included in studies assessing the safety of IBD-related treatment, we excluded these patients in this study to increase the validity of the IBD subtype diagnosis.

Based on the previously emulated trials of SONIC and SUCCESS, [9,10] we excluded patients with tuberculosis, opportunistic infections within the previous 6 months, and patients with a previous history of cancer (excluding nonmelanoma skin cancer) any time prior. Since vedolizumab was only available in patients previously treated with or intolerant to anti-TNF in France during the study period and the majority of patients initiating vedolizumab are previously exposed to immunosuppressants,[17] we could not limit the study to immunosuppressants and biologic-naïve patients. However, we excluded patients previously exposed to other biologics or immunosuppressants than thiopurines, methotrexate, and anti-TNF, i.e., ustekinumab, tofacitinib, natalizumab. In order to select patients treated with only thiopurines combined with vedolizumab, we excluded patients exposed to methotrexate within 60 days prior cohort entry. Finally, the exclusion criteria related to IBD disease activity applied in the replicated trials of SONIC and SUCCESS were considered,[9,10] to minimize differences regarding IBD disease activity across these studies. For both CD and UC cohorts, patients with an ostomy, stricture, abscess, abdominal surgery, within the previous six months were excluded. Additionally, patients with UC hospitalized at vedolizumab initiation were excluded, as patients hospitalized for extensive severe UC were excluded in SUCCESS.

Patients initiating vedolizumab after January 1, 2014, were considered for inclusion, and the cohort entry date was defined as the date of treatment initiation. We considered an incident new user design as vedolizumab initiation was defined as not having used vedolizumab any time prior to first identification in the database. We performed an intention-to-treat analysis, and patients were followed up from the day after the cohort entry date until outcome occurrence, death, 112 days of follow-up (week 16) for patients with UC and 180 days of follow-up (week 26) for patients with CD, similarly as in SONIC and SUCCESS.[3,4] Patients were allowed to enter the study cohort only once.

Treatment groups

Since a majority of patients who are initiating vedolizumab in real life are previously exposed to thiopurines, patients previously exposed to thiopurines were not excluded. Combination therapy was defined as starting vedolizumab with a concomitant exposure of thiopurines within 30 days before vedolizumab initiation. Since thiopurines have a long half-life of several days

and a delayed immunological recovery upon discontinuation of therapy is expected,[18] we extended the wash-out period to 60 days without any thiopurines exposure before vedolizumab initiation for the definition of vedolizumab monotherapy.

Thiopurines exposure was based on the collected days' supply for each prescription fill registered in the US databases. In the French databases, patients were considered as being exposed to thiopurines for one month following delivery, as thiopurines are dispensed by French pharmacies, which are authorized to deliver one month supply of treatment. These definitions were previously used.[9,10,15,19]

Outcome

We used the same outcome definition that was validated in the emulated trials of SONIC and SUCCESS. This outcome definition allowed us to replicate RCTs relative risk of corticosteroids-free clinical remission based on a CD Activity Index less than 150 points without any systemic corticosteroid use in SONIC and a total Mayo score of two points or less, with no individual subscore exceeding one point and without any systemic corticosteroid use in SUCCESS.[9,10] The composite effectiveness outcome measure was based on three surrogate endpoints for treatment failure: (1) hospitalisation or surgery related to CD or UC; (2) treatment switch to another biologic drug (infliximab, adalimumab, certolizumab pegol, golimumab, natalizumab, or ustekinumab) or a small molecule (tofacitinib); or (3) exposure to systemic corticosteroids at week 16 in patients with UC or week 26 in patients with CD. Related codes are summarized in Supplementary Table 2.

Adverse events including serious infections were also assessed based on previously published identification algorithms and hospitalisation not related to IBD during follow-up.[16,20]

Patient characteristics

The same range of covariates assessed in the two emulated trials of SONIC and SUCCESS were assessed.[9,10] Patients previously exposed to anti-TNFs were included in the present study, while they were excluded in the two replicated trials; we therefore additionally assessed anti-TNFs exposure within 180 days before vedolizumab initiation and the number of previous anti-TNF agents was assessed within all data available since first identification in the database.

Baseline patient characteristics and markers of CD and UC phenotype and severity were considered, including demographics and comorbidities (previous serious infections, *Clostridioides difficile* infection, cardiovascular disease, chronic kidney failure, chronic liver disease, chronic pulmonary disease, venous thromboembolism, and diabetes). Comorbidities were assessed in the 180 days before cohort entry in MarketScan and Optum and any time prior to cohort entry in the SNDS. CD phenotype included Montreal phenotype,[21] including

inflammatory (B1), stricturing (B2), and penetrating phenotype (B3), as well as perianal involvement. Hospitalization for complicated CD courses (stricture or abscess) and surgery related to CD occurring more than 180 days before cohort entry were also assessed. CD and UC severity and healthcare use intensity were assessed in the 180 days before cohort entry in all databases. CD and UC severity was assessed by corticosteroids and aminosalicylates exposure, the occurrence of CD-related hospitalization or surgery or UC-related hospitalization, abdominal imaging, gastrointestinal endoscopy, fecal pathogen, and the number of C-reactive protein tests ordered. Healthcare use was assessed by hospitalizations not related to CD or UC and the number of gastroenterologist visits.

Statistical analysis

To control for confounding, we calculated a propensity score (PS) for each patient predicting the probability of initiating vedolizumab and thiopurines combined versus vedolizumab monotherapy with logistic regression, including all measured baseline covariates without further variable selection and the year of cohort entry.[22] We matched treatment groups 1:1 on their PS within a caliper of 0.02 on the PS scale.[23] After matching, standardized differences were calculated to assess the balance between patients exposed to combination therapy and those exposed to vedolizumab monotherapy.[24] After PS matching, Log-binomial regression models were used to estimate adjusted risk ratios (RR) with their 95% CIs comparing the risk of treatment failure associated with combination therapy versus vedolizumab monotherapy.[25] PS and outcome models were separately applied for each IBD subtype and each database. Database-specific RRs were combined separately for each IBD subtype by an inverse variance-weighted, fixed-effects model.[26]

Additional prespecified analyses included secondary analyses assessing the risk of each component of the composite endpoint, and subgroup analyses stratified on previous exposure to anti-TNF, exposure to corticosteroids at vedolizumab initiation, on Montreal phenotype (B1 and B2-B3 combined) and the presence of perianal involvement in patients with CD. Sensitivity analyses were performed to test the robustness of our results. First, variables with an absolute standardized difference greater than 0.1 after PS-matching were included as covariates for further adjustment in log–binomial regression models.[27] Second, we performed a PS matched analysis with a variable ratio up to 1:4 with a caliper of 0.02 on the PS scale. Third, we excluded patients with an enrollment period of less than one year before cohort entry in the US databases. Finally, we performed a post-hoc sensitivity analysis assessing treatment failure at week 26 in patients with UC, to assess a potential delayed response associated with thiopurines at week 26.

Analyses were performed using the validated Aetion Evidence Platform (v4.30) including R(v3.4.2) [28–31] and SAS (v9.4) statistical software (SAS Institute).

Patient involvement

Patients and the public were not involved in the design, conduct, or dissemination plans of this research.

Results

Patient characteristics

A total of 6615 and 6649 patients with CD and UC who initiated vedolizumab were identified across the three databases, respectively. After applying the exclusion criteria (Supplementary Figures 1 and 2), 4674 CD and 5625 UC patients were included. Of those, 829 (18.2%) CD and 1120 (16.8%) UC patients were treated with combination therapy (Supplementary Tables 3 and 4). Among patients included in the combination therapy group, 1828 (93.8%) (CD, n=787 [94.9%]; UC, n=1041 [92.9%]) were exposed to thiopurines more than 30 days before cohort entry.

Overall, 97.0% and 97.1% of patients with CD and UC treated with combination therapy were matched to patients with vedolizumab monotherapy. Among patients treated with vedolizumab monotherapy, 89.8% and 93.2% of patients with CD and UC were able to match with at least one patient treated with combination therapy. After PS matching, the cohorts contained 804 and 1088 pairs of patients with CD and UC, respectively. Anti-TNF agents were previously used in 1343 (83.5%) and 1620 (74.4%) patients with CD and UC, while 515 (32.0%) and 929 (42.7%) patients with CD and UC were treated with corticosteroids at vedolizumab initiation, respectively (Tables 1 and 2). Overall, 96% of the covariates had an absolute standardized difference lower than 0.1 which typically indicates adequate balance.[27] No covariates had an absolute standardized difference greater than 0.2 (Supplementary Figure 3).

Table 1. Characteristics of study patients with Crohn's disease treated with vedolizumab monotherapy or vedolizumab and thiopurines, propensity score-matched with a 1:1 fixed ratio

	MarketScan		Optum		SNDS	
Variable	Vedolizumab monotherapy (n=325)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=211)	Vedolizumab and thiopurines (n=211)	Vedolizumab monotherapy (n=268)	Vedolizumab and thiopurines (n=268)
Age, mean (SD), year	40.4 (13.3)	41.2 (12.7)	43.3 (16.2)	43.2 (14.6)	35.3 (11.9)	36.4 (12.2)
Sex						
Male	134 (41.2)	128 (39.4)	90 (42.7)	91 (43.1)	116 (43.3)	103 (38.4)
Female	191 (58.8)	197 (60.6)	121 (57.3)	120 (56.9)	152 (56.7)	165 (61.6)
Crohn's disease duration, mean (SD), year	-	-	-	-	9.1 (6.2)	9.6 (6.4)
Montreal phenotype						
B1	163 (50.2)	157 (48.3)	100 (47.4)	103 (48.8)	203 (75.7)	189 (70.5)
B2	78 (24.0)	85 (26.2)	47 (22.3)	50 (23.7)	39 (14.6)	54 (20.1)
B3	84 (25.8)	83 (25.5)	64 (30.3)	58 (27.5)	26 (9.7)	25 (9.3)
Perianal Crohn's disease	39 (12.0)	40 (12.3)	22 (10.4)	18 (8.5)	80 (29.9)	84 (31.3)

Table 1. Characteristics of study patients with Crohn's disease treated with vedolizumab monotherapy or vedolizumab and thiopurines, propensity score-matched with a 1:1 fixed ratio (continued)

	MarketScan		Optum		SNDS	
	Vedolizumab monotherapy (n=325)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=211)	Vedolizumab and thiopurines (n=211)	Vedolizumab monotherapy (n=268)	Vedolizumab and thiopurines (n=268)
Crohn's disease complicated disease course						
More than 180 days before cohort entry	33 (10.2)	41 (12.6)	25 (11.8)	18 (8.5)	66 (24.6)	63 (23.5)
Surgery related to Crohn's disease						
More than 180 days before cohort entry	50 (15.4)	54 (16.6)	34 (16.1)	29 (13.7)	102 (38.1)	106 (39.6)
Number of prior anti-TNFs						
0	65 (20.0)	69 (21.2)	65 (30.8)	66 (31.3)	-	-
1	167 (51.4)	157 (48.3)	102 (48.3)	101 (47.9)	76 (28.4)	81 (30.2)
2	72 (22.2)	81 (24.9)	34 (16.1)	33 (15.6)	166 (61.9)	167 (62.3)
3	21 (6.5)	18 (5.5)	10 (4.7)	11 (5.2)	26 (9.7)	20 (7.5)
Anti-TNF within 180 days before cohort entry	172 (52.9)	171 (52.6)	102 (48.3)	107 (50.7)	215 (80.2)	214 (79.9)
Corticosteroids (oral)						
within 180 days before cohort entry	214 (65.8)	217 (66.8)	130 (61.6)	134 (63.5)	156 (58.2)	140 (52.2)
at cohort entry	102 (31.4)	98 (30.2)	62 (29.4)	69 (32.7)	99 (36.9)	85 (31.7)
Aminosalicylates (oral)	151 (46.5)	147 (45.2)	82 (38.9)	84 (39.8)	176 (65.7)	169 (63.1)
Opioids	140 (43.1)	131 (40.3)	87 (41.2)	86 (40.8)	32 (11.9)	33 (12.3)
Crohn's disease activity assessment †						
Hospitalisation related to Crohn's disease	32 (9.8)	25 (7.7)	11 (5.2)	12 (5.7)	55 (20.5)	57 (21.3)
Abdominal imaging	113 (34.8)	113 (34.8)	91 (43.1)	89 (42.2)	130 (48.5)	120 (44.8)
Lower GI endoscopy	163 (50.2)	153 (47.1)	92 (43.6)	90 (42.7)	130 (48.5)	129 (48.1)
Upper GI endoscopy	45 (13.8)	46 (14.2)	33 (15.6)	27 (12.8)	46 (17.2)	45 (16.8)
CRP tests ordered, mean (SD)	1.23 (1.47)	1.28 (1.63)	1.78 (3.98)	1.76 (2.07)	3.38 (2.72)	3.53 (2.67)
Fecal pathogen tests ordered	68 (20.9)	60 (18.5)	42 (19.9)	45 (21.3)	46 (17.2)	39 (14.6)
Comorbidities						
Clostridioides difficile infection	8 (2.5)	5 (1.5)	1 (0.5)	3 (1.4)	9 (3.4)	5 (1.9)
Serious infection	13 (4.0)	6 (1.8)	6 (2.8)	4 (1.9)	4 (1.5)	4 (1.5)
Cardiovascular disease	14 (4.3)	16 (4.9)	25 (11.8)	23 (10.9)	20 (7.5)	22 (8.2)
Chronic kidney failure	2 (0.6)	4 (1.2)	12 (5.7)	11 (5.2)	5 (1.9)	5 (1.9)
Chronic liver disease	3 (0.9)	5 (1.5)	19 (9.0)	16 (7.6)	6 (2.2)	3 (1.1)
Chronic pulmonary disease	44 (13.5)	44 (13.5)	53 (25.1)	41 (19.4)	78 (29.1)	85 (31.7)
Venous thromboembolism	7 (2.2)	7 (2.2)	9 (4.3)	7 (3.3)	7 (2.6)	11 (4.1)
Diabetes	15 (4.6)	16 (4.9)	17 (8.1)	15 (7.1)	10 (3.7)	9 (3.4)
Healthcare use characteristics †						
Hospitalizations not related to Crohn's disease	32 (9.8)	20 (6.2)	27 (12.8)	21 (10.0)	18 (6.7)	23 (8.6)
Gastroenterologist visits, mean (SD)	5.69 (7.41)	5.42 (7.13)	7.06 (8.13)	6.69 (9.80)	3.74 (4.89)	3.71 (5.76)

Data are n (%) unless otherwise stated. † Assessed within 180 days before cohort entry

Table 2. Characteristics of study patients with ulcerative colitis treated with vedolizumab monotherapy or vedolizumab and thiopurines, propensity score-matched with a 1:1 fixed ratio

	MarketScan		Optum		SNDS	
Variable	Vedolizumab monotherapy (n=440)	Vedolizumab and thiopurines (n=440)	Vedolizumab monotherapy (n=325)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=323)	Vedolizumab and thiopurines (n=323)
Age, mean (SD), year	41.6 (14.0)	41.3 (13.6)	43.4 (16.2)	43.2 (15.6)	39.3 (14.7)	40.3 (13.8)
Sex						
Male	238 (54.1)	231 (52.5)	162 (49.8)	155 (47.7)	167 (51.7)	172 (53.3)
Female	202 (45.9)	209 (47.5)	163 (50.2)	170 (52.3)	156 (48.3)	151 (46.7)
Ulcerative colitis disease duration (years), mean (SD)	-	-	-	-	6.6 (5.2)	6.9 (5.3)
Number of prior anti-TNFs						
0	141 (32.0)	135 (30.7)	142 (43.7)	138 (42.5)	-	-
1	218 (49.5)	223 (50.7)	146 (44.9)	145 (44.6)	148 (45.8)	154 (47.7)
2	70 (15.9)	71 (16.1)	35 (10.8)	39 (12.0)	157 (48.6)	153 (47.4)
3	11 (2.5)	11 (2.5)	2 (0.6)	3 (0.9)	18 (5.6)	16 (5.0)
Anti-TNF within 180 days before cohort entry	243 (55.2)	242 (55.0)	153 (47.1)	158 (48.6)	291 (90.1)	288 (89.2)
Aminosalicylates (oral) at cohort entry	164 (37.3)	167 (38.0)	116 (35.7)	119 (36.6)	93 (28.8)	91 (28.2)
Corticosteroids (oral)						
within 180 days before cohort entry	339 (77.0)	341 (77.5)	233 (71.7)	240 (73.8)	227 (70.3)	224 (69.3)
at cohort entry	193 (43.9)	189 (43.0)	130 (40.0)	134 (41.2)	143 (44.3)	140 (43.3)
Opioids	156 (35.5)	149 (33.9)	51 (15.7)	55 (16.9)	23 (7.1)	26 (8.0)
Ulcerative colitis activity assessment †						
Hospitalization related to ulcerative colitis	43 (9.8)	41 (9.3)	25 (7.7)	28 (8.6)	48 (14.9)	49 (15.2)
Abdominal imaging	70 (15.9)	74 (16.8)	38 (11.7)	54 (16.6)	49 (15.2)	56 (17.3)
Lower GI endoscopy	241 (54.8)	241 (54.8)	193 (59.4)	195 (60.0)	239 (74.0)	230 (71.2)
Upper GI endoscopy	18 (4.1)	21 (4.8)	18 (5.5)	17 (5.2)	23 (7.1)	27 (8.4)
CRP tests ordered, mean (SD)	1.41 (1.62)	1.33 (1.68)	1.67 (1.92)	1.60 (1.91)	4.02 (2.75)	4.12 (3.21)
Fecal pathogen tests ordered	173 (39.3)	177 (40.2)	128 (39.4)	133 (40.9)	84 (26.0)	89 (27.6)
Comorbidities						
Clostridioides difficile infection	32 (7.3)	29 (6.6)	11 (3.4)	13 (4.0)	13 (4.0)	13 (4.0)
Serious infection	5 (1.1)	3 (0.7)	3 (0.9)	5 (1.5)	3 (0.9)	5 (1.5)
Cardiovascular disease	29 (6.6)	25 (5.7)	29 (8.9)	29 (8.9)	27 (8.4)	27 (8.4)
Chronic kidney failure	9 (2.0)	6 (1.4)	4 (1.2)	5 (1.5)	1 (0.3)	3 (0.9)
Chronic liver disease	4 (0.9)	2 (0.5)	10 (3.1)	17 (5.2)	7 (2.2)	6 (1.9)
Chronic pulmonary disease	45 (10.2)	52 (11.8)	31 (9.5)	38 (11.7)	64 (19.8)	73 (22.6)
Venous thromboembolism	3 (0.7)	6 (1.4)	11 (3.4)	15 (4.6)	9 (2.8)	9 (2.8)
Diabetes	42 (9.5)	37 (8.4)	26 (8.0)	32 (9.8)	20 (6.2)	26 (8.0)
Healthcare use characteristics †						
Hospitalizations not related to ulcerative colitis	26 (5.9)	20 (4.5)	14 (4.3)	20 (6.2)	19 (5.9)	15 (4.6)
Gastroenterologist visits, mean (SD)	5.81 (6.74)	5.88 (7.72)	6.43 (7.90)	6.65 (7.89)	5.48 (6.52)	5.47 (6.93)

Data are n (%) unless otherwise stated. † Assessed within 180 days before cohort entry

Risk of treatment failure

Crohn's disease

After PS-matching, treatment failure at week 26 occurred in 236 (29.3%) and 376 (34.3%) patients initiating combination therapy and vedolizumab monotherapy, respectively (Figure 1). Among patients with treatment failure, hospitalization or surgery related to CD was the most frequent outcome, accounting for 47% and 43% of outcomes in patients initiating combination therapy and vedolizumab monotherapy. The proportion of patients with treatment failure according to databases after PS-matching is provided in Supplementary Table 5.

Patients initiating combination therapy had a 15% decreased risk of treatment failure compared to patients initiating infliximab monotherapy (RR 0.85, 95%CI 0.74 to 0.98) (Figure 2). Results were similar across the three databases (RR 0.87, 95%CI 0.68 to 1.12, RR 0.88, 95%CI 0.64 to 1.21, and RR 0.83, 95%CI 0.68 to 0.98) in MarketScan, Optum, and SNDS, respectively). A similar trend was observed for all secondary endpoints, notably for hospitalization or surgery related to CD (RR 0.78, 95% CI 0.62 to 0.99) (Figure 2).

Ulcerative colitis

In the PS matched cohort, 236 (21.7%) and 263 (24.2%) patients were in treatment failure at week 16 after initiating combination therapy and vedolizumab monotherapy, respectively. Exposure to corticosteroids at week 16 was the most frequent outcome, accounting for 62% and 66% of outcomes in patients initiating combination therapy and vedolizumab monotherapy. Treatment switch only accounted for 19% and 27% of outcomes in patients initiating combination therapy and vedolizumab monotherapy.

The risk of treatment failure differed little between combination therapy and vedolizumab monotherapy (RR 0.90, 95%CI 0.77 to 1.05), with similar findings across all secondary endpoints (Figure 3).

Secondary analysis, subgroup and sensitivity analyses

Rates of serious infections and hospitalisations not related to IBD did not differ between the two treatment groups. (Supplementary Table 6)

Overall, we observed no meaningful variation in treatment failure risks across subgroups (Figure 4). While the risk of treatment failure associated with combination therapy versus vedolizumab monotherapy appeared to be lower in anti-TNF experienced compared to anti-TNF naïve patients with CD (RR 0.90, 95%CI 0.77 to 1.05, and RR 1.26, 95%CI 0.71 to 2.25, respectively), this trend was not observed in anti-TNF experienced compared to anti-TNF naïve patients with UC (RR 0.93, 95%CI 0.79 to 1.10, and RR 0.98, 95%CI 0.65 to 1.46,

respectively). In patients treated with corticosteroids at vedolizumab initiation, the combined RR was 0.87 (95%CI 0.71 to 1.08) and 1.01 (95%CI 0.83 to 1.23) in CD and UC, respectively.

In patients with CD, the combined RR for treatment failure associated with combination therapy versus vedolizumab monotherapy was 0.95 (95%CI 0.78 to 1.15) and 0.87 (95%CI 0.69 to 1.11) in patients with inflammatory phenotype and patients with stricturing or penetrating phenotypes, respectively. The various sensitivity analyses yielded consistent results (Supplementary Table 7). Extending follow-up to week 26 in UC did not modify the results (RR 0.94, 95%CI 0.83 to 1.06).

Figure 1. Outcomes, propensity score-matched with a 1:1 fixed ratio in Crohn's disease (A) and ulcerative colitis (B)

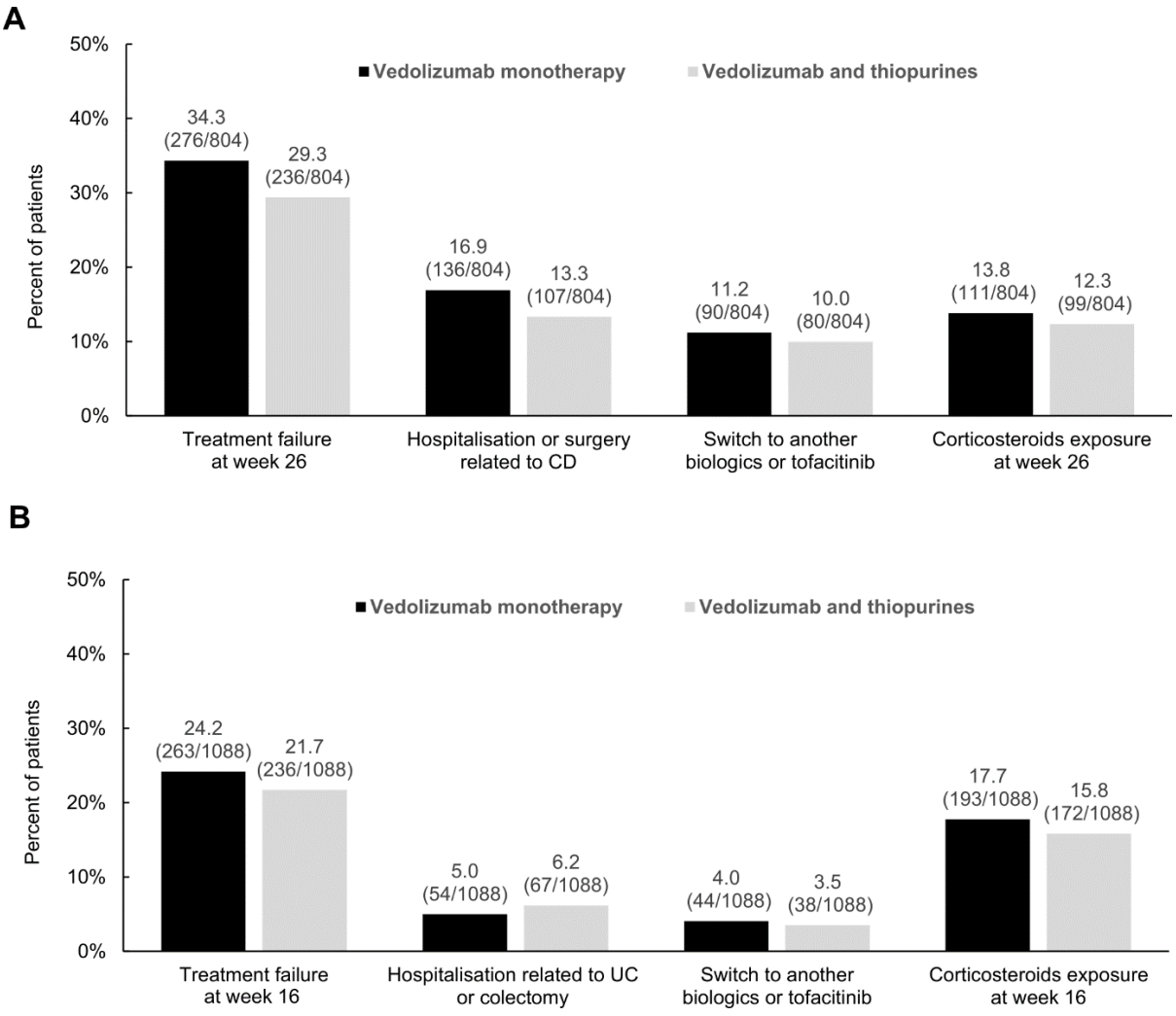


Figure 2. Risk ratios for treatment failure and for each individual component of the composite outcome associated with combination therapy compared to vedolizumab monotherapy in Crohn's disease

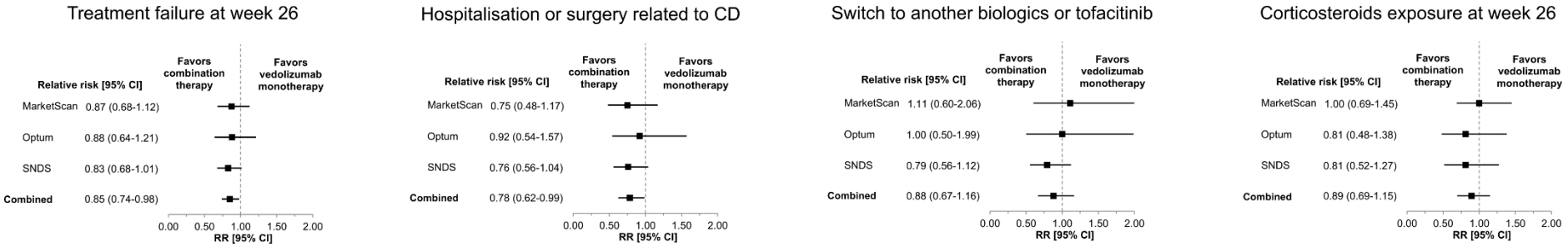


Figure 3. Risk ratios for treatment failure and for each individual component of the composite outcome associated with combination therapy compared to vedolizumab monotherapy in ulcerative colitis

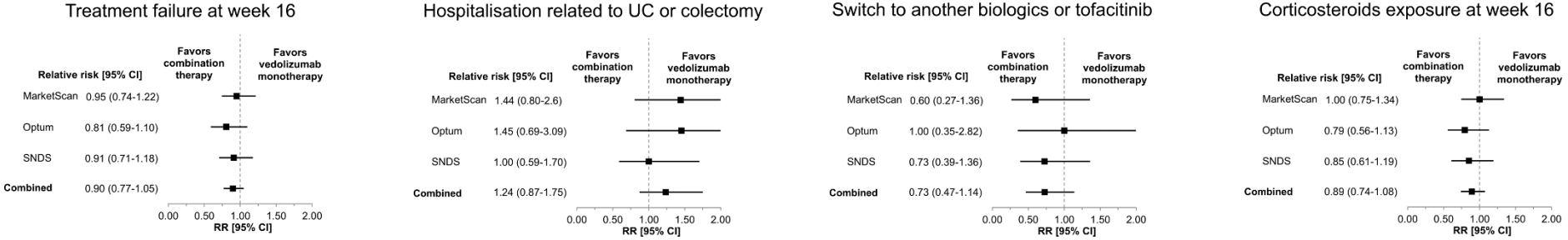
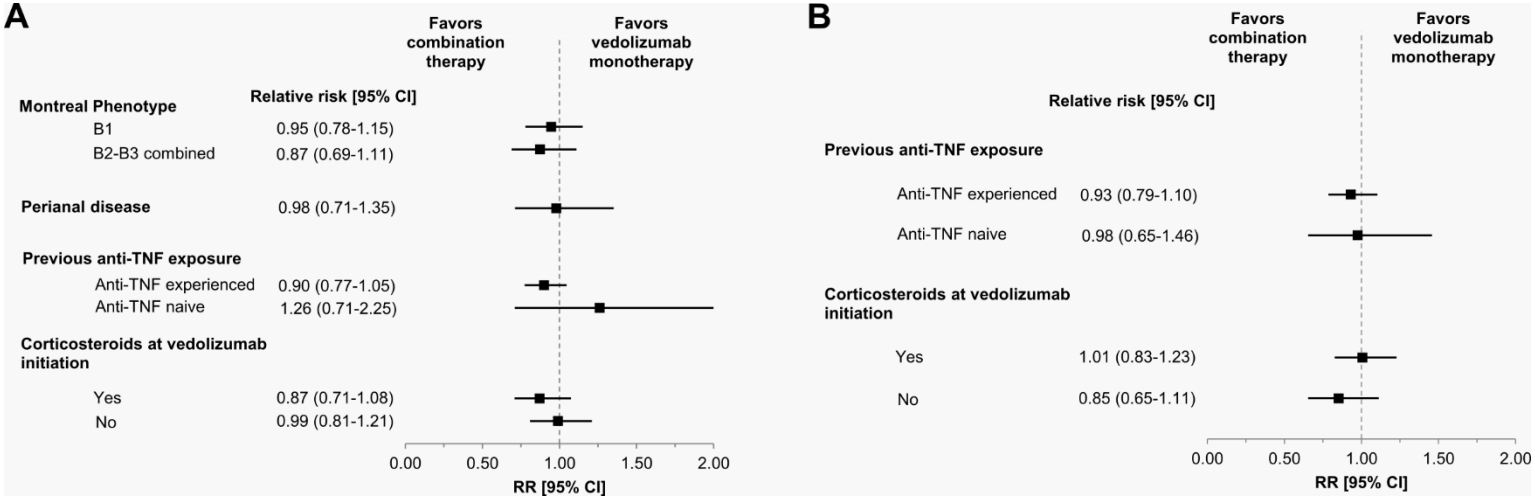


Figure 4. Risk ratios for treatment failure associated with combination therapy with vedolizumab and thiopurines compared to vedolizumab monotherapy in Crohn's disease (A) and ulcerative colitis (B): subgroup analysis



Discussion

Using three large population-based cohorts in the U.S. and France, we emulated two hypothetical target trials comparing the effectiveness of combination therapy with vedolizumab and thiopurines against vedolizumab monotherapy in patients with CD and UC. While combination therapy was associated with a lower risk of treatment failure compared to vedolizumab monotherapy in CD, this effect was possibly observed to a lesser extent in patients with UC. Findings were consistent across databases and for individual components of the composite outcome.

Only two studies assessed the impact of adding a co-immunosuppressant with vedolizumab in IBD. First, a meta-analysis based on 16 studies, among which none were aimed to address this question with adjustment for disease severity, reported no benefit of concomitant immunosuppressive therapy on clinical benefit in either CD (odds ratio [OR] 0.84; 95% CI, 0.53-1.33) or UC (OR 0.92; 95% CI, 0.60-1.41) with wide CIs. In a recent study based on three IBD tertiary care centers, clinical response at week 14 was not different in patients with IBD treated with vedolizumab and a co-immunosuppressant combined compared to vedolizumab monotherapy (OR 0.91, 95%CI 0.56 to 1.47). However, this effect differed according to IBD subtype (CD, OR 1.38, 95%CI 0.63 to 3.00, UC, OR 0.63, 95%CI 0.33 to 1.20), yet the effect estimates had substantial uncertainty given the small study size. Interestingly, co-immunosuppressant exposure tends to be associated with a lower risk of serious infections in CD (hazard ratio [HR] 0.78, 95%CI 0.54 to 1.13) but not in UC (HR 1.68, 95%CI 0.98 to 2.87) in a study based on vedolizumab phase III trials.[32] Since IBD disease activity is an independent risk factor for serious infections, these findings may be related to effectiveness differences of combination therapy compared to vedolizumab monotherapy between IBD subtypes. Our findings are in line with these studies, while we included more than 10,000 patients starting vedolizumab and the number of PS-matched patients treated with vedolizumab and thiopurines was two-fold higher than that of the meta-analysis. This allows us to perform two dedicated target trials according to the IBD subtype with an adequate sample size.

Although statistically not significant, the magnitude in relative risk reduction associated with combination therapy was 10% at week 16 in patients with UC, compared to 15% at week 26 in patients with CD. In a post-hoc sensitivity analysis, we extended the follow-up to week 26 in patients with UC, to assess a potential delayed response of thiopurines, which was not supported by the results with a magnitude in relative risk reduction of 5%. The relative risk reduction of 15% of treatment failure associated with combination therapy should be interpreted in light of the relative risk reduction of treatment failure reported with the

combination of anti-TNF and thiopurines. In the SONIC trial, the relative risk reduction associated with the combination of infliximab and thiopurines compared to infliximab monotherapy was of 22% (RR 0.78, 95%CI 0.62 to 0.97),[3] which, along with the decreased risk of immunogenicity, led to recommend combination therapy in patients with moderate-to-severe CD initiating infliximab.[33] It highlights the clinical relevance of the relative risk reduction observed with the combination of vedolizumab and thiopurines in patients with CD.

Adding thiopurines to vedolizumab was associated with a lower risk of treatment failure in CD, and possibly to a lesser extent in UC. The mechanism of action for incremental effectiveness by adding thiopurines to vedolizumab remains to be elucidated. Vedolizumab clearance may not be influenced by the addition of an immunosuppressant and the development of anti-drug antibodies is uncommon.[34] Vedolizumab effectiveness may differ according to IBD subtypes with potential lower effectiveness in anti-TNF experienced patients with CD,[35] the incremental effectiveness of thiopurines observed in our study may be related to its individual effectiveness per se. Notably, we observed a trend for higher effectiveness of combination therapy in anti-TNF experienced compared to anti-TNF naïve patients with CD.

Calibration of RWE studies against treatment effect assessed in RCTs allows evaluating whether RWE can support causal conclusions if conducted using robust methodology.[31] We first replicated the findings of the SONIC and SUCCESS trials assessing the effectiveness of combination therapy with infliximab and thiopurines compared to infliximab monotherapy in patients with IBD. [9,10] Using this approach, we were able to develop an effectiveness outcome measure that could be used in future studies assessing the effectiveness of IBD related treatment, notably add-on strategies with other treatments than infliximab. Similarly, we considered the same exclusion criteria related to IBD disease activity and the same covariates in the propensity score model, only adding in the PS model the number of previous anti-TNF agents and previous exposure to anti-TNF in the 180 days before vedolizumab initiation, since we included anti-TNF experienced patients and previous anti-TNF exposure has an impact on vedolizumab effectiveness.[36] This robust methodology strengthens our findings.

We used PS matching, as the PS focuses directly on the indications for use and non-use of the drug under study compared to conventional multivariable methods. Discarding unmatched observations is a consequence of limited overlap in patients' covariate distributions and as such increase validity and reduce generalizability to those patients that have treatment equipoise.[37] In this study, 97% of patients treated with combination therapy were matched to patients with vedolizumab monotherapy.

One of the main strengths of our study is the generalizability and large size as we used two large U.S. and one French nationwide population-based cohorts, which allows assessing not only the impact of differences in population selection, data collection and follow-up between the databases but also treatment effectiveness in different healthcare schemes and potential prescribing patterns. While healthcare is guaranteed for all French residents and patients are followed from birth to emigration or death in the French database, the US databases only included commercially insured patients and health insurance enrollment changes may reduce the enrollment period to assess covariates. Results were consistent across databases, which suggests that these differences had a minimal impact on the treatment estimate observed.

Some limitations should be noted. We were not able to exclude prevalent users of thiopurines in the combination therapy group, since the vast majority of patients exposed to vedolizumab are previously treated with thiopurines in a real-life setting. In our study, prevalent users of thiopurines accounted for 94% of patients included in the combination therapy group before PS-matching. However, we applied a stringent definition to define vedolizumab monotherapy with a mandatory wash-out period of 60 days without any thiopurines exposure. Thiopurines dose and 6-tioguanine levels were not available. Further research is needed to assess if a specific threshold is applied to vedolizumab.[38] There is no validation study assessing the accuracy of the Montreal classification in the U.S or French databases. However, assessing IBD phenotype may decrease the potential for confounding by indication.[36] Endoscopic and histological data were not available, and residual confounding by these factors cannot be entirely ruled out. To minimize potential confounding by indication, we used a previously validated definition of treatment failure and adjusted for IBD disease severity similarly as in the two replicated trials of SONIC and SUCCESS.[9,10] Follow-up was censored at week 26 and 16 in CD and UC.[3,4] The impact of continuing thiopurines during a longer period should be further assessed.

In summary, this study based on three large population-based cohorts of patients with IBD in both the U.S. and France provides evidence that combination therapy with vedolizumab and thiopurines is more effective compared to vedolizumab monotherapy in patients with CD and possibly less so with UC. These findings will help guide clinical decision-making in patients with IBD starting vedolizumab.

Figure Legends:

Figure 1. Outcomes, propensity score-matched with a 1:1 fixed ratio in Crohn's disease (A) and ulcerative colitis (B)

Figure 2. Risk ratios for treatment failure and for each individual component of the composite outcome associated with combination therapy compared to vedolizumab monotherapy in Crohn's disease

Figure 3. Risk ratios for treatment failure and for each individual component of the composite outcome associated with combination therapy compared to vedolizumab monotherapy in ulcerative colitis

Figure 4. Risk ratios for treatment failure associated with combination therapy with vedolizumab and thiopurines compared to vedolizumab monotherapy in Crohn's disease (A) and ulcerative colitis (B): subgroup analysis

Contributors:

Dr Kirchgesner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Kirchgesner, Schneeweiss S., Kim. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Kirchgesner. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Kirchgesner, Schneeweiss S., Kim. Supervision: Kirchgesner, Schneeweiss S., Kim.

Conflict of Interest Disclosures:

The authors disclose the following: Julien Kirchgesner received research support from the French National Society of Gastroenterology (SNFGE), and has received consulting fees from Roche and Pfizer, and research support from Abbvie for unrelates studies. Rishi J. Desai has received research support to the Brigham and Women's Hospital from Novartis, Vertex, and Bayer for unrelated studies. Laurent Beaugerie has received consulting fees from Janssen, Pfizer and Allergan, lecture fees from Abbvie, Janssen, MSD, Ferring Pharmaceuticals, Mayoly-Spendler, Takeda, and Tillots, and research support from Abbott, Ferring Pharmaceuticals, Hospira-Pfizer, Janssen, MSD, Takeda, and Tillots for unrelated studies. Sebastian Schneeweiss is participating in investigator-initiated grants to the Brigham and Women's Hospital from Bayer, Vertex, and Boehringer Ingelheim unrelated to the topic of this study. He is a consultant to Aetion Inc., a software manufacturer of which he owns equity. Seoyoung C. Kim has received research support to the Brigham and Women's Hospital from Roche, AbbVie, and Bristol-Myers Squibb for unrelated studies.

Funding:

The investigators conducted the research independently through funding from internal sources of the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School. Julien Kirchgesner received research support (Robert Tournut 2019 grant) from the French National Society of Gastroenterology (SNFGE).

References

1 Feagan BG, Rutgeerts P, Sands BE, *et al.* Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2013;**369**:699–710.

2 Sandborn WJ, Feagan BG, Rutgeerts P, *et al.* Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med* 2013;**369**:711–21.

3 Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.

4 Panaccione R, Ghosh S, Middleton S, *et al.* Combination Therapy With Infliximab and Azathioprine Is Superior to Monotherapy With Either Agent in Ulcerative Colitis. *Gastroenterology* 2014;**146**:392-400.e3.

5 Yzet C, Diouf M, Singh S, *et al.* No Benefit of Concomitant Immunomodulator Therapy on Efficacy of Biologics That Are Not Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Diseases: A Meta-analysis. *Clin Gastroenterol Hepatol* 2021;**19**:668-679.e8.

6 Hu A, Kotze PG, Burgevin A, *et al.* Combination Therapy Does Not Improve Rate of Clinical or Endoscopic Remission in Patients with Inflammatory Bowel Diseases Treated With Vedolizumab or Ustekinumab. *Clin Gastroenterol Hepatol* 2021;**19**:1366-1376.e2.

7 Clinicaltrials.gov. Studies found for: vedolizumab. https://clinicaltrials.gov/ct2/results?cond=&term=vedolizumab&cntry=&state=&city=&dist= (accessed 7 Dec2021).

8 Schneeweiss S, Eichler H-G, Garcia-Altes A, *et al.* Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making. *Clin Pharmacol Ther* 2016;**100**:633–46.

9 Kirchgesner J, Desai RJ, Beaugerie L, *et al.* Calibrating Real-World Evidence Studies Against Randomized Trials: Treatment Effectiveness of Infliximab in Crohn's Disease. *Clin Pharmacol Ther* 2022;**111**:179–86.

10 Kirchgesner J, Desai RJ, Schneeweiss MC, *et al.* Emulation of a randomized controlled trial in ulcerative colitis with US and French claims data: Infliximab with thiopurines compared to infliximab monotherapy. *Pharmacoepidemiol Drug Saf* 2022;**31**:167–75.

11 Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 2016;**183**:758–64.

12 Franklin JM, Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? *Clin Pharmacol Ther* 2017;**102**:924–33.

13 Bezin J, Duong M, Lassalle R, *et al.* The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017;**26**:954–62.

14 Kirchgesner J, Lemaitre M, Rudnichi A, *et al.* Therapeutic management of inflammatory bowel disease in real-life practice in the current era of anti-TNF agents: analysis of the French administrative health databases 2009-2014. *Aliment Pharmacol Ther* 2017;**45**:37–49.

15 Lemaitre M, Kirchgesner J, Rudnichi A, *et al.* Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. *JAMA* 2017;**318**:1679–86.

16 Kirchgesner J, Lemaitre M, Carrat F, *et al.* Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology* 2018;**155**:337-346.e10.

17 Haute Autorité de Santé - ENTYVIO (vedolizumab), anti-intégrine α4β7. https://www.has-sante.fr/portail/jcms/c_2818013/fr/entyvio-vedolizumab-anti-integrine-47 (accessed 13 Jan2019).

18 Ben-Horin S, Van Assche G, Chowers Y, *et al.* Pharmacokinetics and Immune Reconstitution Following Discontinuation of Thiopurine Analogues: Implications for Drug Withdrawal Strategies. *J Crohns Colitis* 2018;**12**:1410–7.

19 Kirchgesner J, Nyboe Andersen N, Carrat F, *et al.* Risk of acute arterial events associated with treatment of inflammatory bowel diseases: nationwide French cohort study. *Gut* 2020;**69**:852–8.

20 Kirchgesner J, Desai RJ, Beaugerie L, *et al.* Risk of Serious Infections With Vedolizumab Versus Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2022;**20**:314-324.e16.

21 Satsangi J, Silverberg MS, Vermeire S, *et al.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.

22 Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol* 2006;**98**:253–9.

23 Rassen JA, Shelat AA, Myers J, *et al.* One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf* 2012;**21**:69–80.

24 Franklin JM, Rassen JA, Ackermann D, *et al.* Metrics for covariate balance in cohort studies of causal effects. *Stat Med* 2014;**33**:1685–99.

25 Robbins AS, Chao SY, Fonseca VP. What's the relative risk? A method to directly estimate risk ratios in cohort studies of common outcomes. *Ann Epidemiol* 2002;**12**:452–4.

26 *Manager R. (RevMan) [Computer program]. Version 5.3. Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014.*

27 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;**34**:3661–79.

28 Aetion Evidence Platform® (2020). Software for real-world data analysis. Aetion, Inc. Aetion. https://aetion.com/ (accessed 7 Jan2021).

29 Wang SV, Verpillat P, Rassen JA, *et al.* Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases. *Clin Pharmacol Ther* 2016;**99**:325–32.

30 Patorno E, Schneeweiss S, Gopalakrishnan C, *et al.* Using Real-World Data to Predict Findings of an Ongoing Phase IV Cardiovascular Outcome Trial: Cardiovascular Safety of Linagliptin Versus Glimepiride. *Diabetes Care* 2019;**42**:2204–10.

31 Franklin JM, Patorno E, Desai RJ, *et al.* Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies: First Results From the RCT DUPLICATE Initiative. *Circulation* 2021;**143**:1002–13.

32 Colombel J-F, Sands BE, Rutgeerts P, *et al.* The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2017;**66**:839–51.

33 Torres J, Bonovas S, Doherty G, *et al.* ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis* 2020;**14**:4–22.

34 Rosario M, Dirks NL, Gastonguay MR, *et al.* Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther* 2015;**42**:188–202.

35 Sands BE, Feagan BG, Rutgeerts P, *et al.* Effects of Vedolizumab Induction Therapy for Patients With Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed. *Gastroenterology* 2014;**147**:618-627.e3.

36 Barré A, Colombel J-F, Ungaro R. Review article: predictors of response to vedolizumab and ustekinumab in inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;**47**:896–905.

37 Glynn RJ, Lunt M, Rothman KJ, *et al.* Comparison of alternative approaches to trim subjects in the tails of the propensity score distribution. *Pharmacoepidemiol Drug Saf* 2019;**28**:1290–8.

38 Roblin X, Boschetti G, Williet N, *et al.* Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Aliment Pharmacol Ther* 2017;**46**:142–9.

Supplementary Material

Supplementary Table 1. Specification and emulation of a target trial studying the effectiveness of vedolizumab and thiopurines combined compared to vedolizumab monotherapy in patients with Crohn's disease and ulcerative colitis

Component	Target trial	Emulation
Eligibility	Age ≥ 18 UC: diagnosis of UC, not hospitalized for extensive severe UC at baseline CD: diagnosis of CD No tuberculosis or opportunistic infections within the past 6 months No history of cancer (excluding non-melanoma skin cancer) No exposure to ustekinumab, tofacitinib, or natalizumab No exposure to methotrexate within the past 60 days No ostomy, stricture, abscess, abdominal surgery, within the past 6 months At least 180 days of look-back period* Baseline is defined as the day of vedolizumab initiation	Same as for the target trial Inclusion and exclusion criteria were based on diagnosis codes and treatment deliveries Patients with UC hospitalized at baseline were excluded
Treatment strategies	(1) Initiation of vedolizumab combined with thiopurines (Combination therapy) (2) Initiation of vedolizumab without any co-immunosuppressant (Vedolizumab monotherapy)	Same as for the target trial We defined the date of vedolizumab and thiopurines initiations to be the first date of treatment perfusion or delivery, respectively Combination therapy was defined as starting vedolizumab with a concomitant exposure of thiopurines within 30 days before vedolizumab initiation. A wash-out period of 60 days without any thiopurines exposure before vedolizumab initiation was required for the definition of vedolizumab monotherapy.
Treatment assignment	Individuals are randomly assigned to a strategy at baseline and will be aware of the strategy to which they have been assigned	We classified individuals according to the strategy that their data were compatible with at baseline and attempted to emulate randomization by adjusting for baseline confounders
Primary end point	CD: corticosteroid-free clinical remission at week 26, defined by a Crohn's Disease Activity Index (CDAI) less than 150 points without any systemic corticosteroid use. UC: corticosteroid-free clinical remission at week 16, defined by a total Mayo score of two points or less, with no individual subscore exceeding one point and without any systemic corticosteroid use.	Since the CDAI and Mayo score are not available in the US or French healthcare databases, we developed a composite effectiveness outcome measure based on three surrogate endpoints for treatment failure: (1) hospitalisation or surgery related to CD / hospitalisation or colectomy related to UC; (2) treatment switch to another biologics (infliximab, adalimumab, certolizumab pegol, golimumab, natalizumab, vedolizumab, ustekinumab) or small molecules (tofacitinib); or (3) exposure to systemic corticosteroids at week 26 (CD) or 16 (UC). These outcome measures were previously calibrated by replicating the SONIC and SUCCESS trials using the same databases.

Supplementary Table 1. Specification and emulation of a target trial studying the effectiveness of vedolizumab and thiopurines combined compared to vedolizumab monotherapy in patients with Crohn's disease and ulcerative colitis (continued)

Follow-up	Starts from the day after baseline until outcome occurrence, death, 112 days of follow-up (week 16) for patients with UC and 180 days of follow-up (week 26) for patients with CD.	Same as for the target trial
Causal contrast	Intention-to-treat effect	Observational analog of intention-to-treat
Statistical analysis	Intention-to-treat analysis Subgroup analyses by previous exposure to anti-TNF, corticosteroids at baseline CD: Subgroup analyses according to Montreal phenotype (B1 and B2-B3 combined) and the presence of perianal disease	Same intention-to-treat analyses with additional adjustment for baseline covariates Same subgroup analyses

* Required for U.S databases
Abbreviations: CD, Crohn's disease: UC: ulcerative colitis.

Supplementary Table 2. Effectiveness outcome measure with related codes

Outcomes	ICD-10	ICD-9	Procedures	Anatomical Therapeutic Chemical (ATC) classification system code
Crohn's disease				
Hospitalization or surgery related to Crohn's disease	K50; K56; K60; K61; K62.4; K62.5; K63.0; K63.1; K63.2; K65.0; K65.1; K92.2; R10	555; 560; 565; 566; 567.21; 567.22; 567.29; 569.2; 569.3; 569.5; 569.81; 569.83; 578.9; 789.0	Abdominal and perineal surgery	-
Switch to another biologics or tofacitinib	-	-	-	L04AB02 (infliximab), L04AB04 (adalimumab), L04AB05 (certolizumab pegol), L04AB06 (golimumab), L04AA23 (natalizumab), L04AC05 (ustekinumab), or L04AA29 (tofacitinib)
Corticosteroids exposure at week 26	-	-	-	H02AB04 (methylprednisolone); H02AB06 (prednisolone, only IV or oral intake); H02AB07 (prednisone, only IV or oral intake); H02AB10 (cortisone, only IV or oral intake); A07EA06 (budesonide, only intestinal release)
Ulcerative colitis				
Hospitalization or related to ulcerative colitis or colectomy	K51; K56; K60; K62.5; K63.0; K63.1; K63.2; K65.0; K65.1; K92.2; R10	556; 560; 567.21; 567.22; 567.29; 569.3; 569.5; 569.81; 569.83; 578.9; 789.0	Colectomy	-
Switch to another biologics or tofacitinib	-	-	-	L04AB02 (infliximab), L04AB04 (adalimumab), L04AB05 (certolizumab pegol), L04AB06 (golimumab), L04AA23 (natalizumab), L04AC05 (ustekinumab), or L04AA29 (tofacitinib)
Corticosteroids exposure at week 26	-	-	-	H02AB04 (methylprednisolone); H02AB06 (prednisolone, only IV or oral intake); H02AB07 (prednisone, only IV or oral intake); H02AB10 (cortisone, only IV or oral intake)

Supplementary Table 3. Characteristics of study patients with Crohn's disease treated with vedolizumab monotherapy or vedolizumab and thiopurines, before propensity score-matching

	MarketScan		Optum		SNDS	
Variable	Vedolizumab monotherapy (n=1471)	Vedolizumab and thiopurines (n=326)	Vedolizumab monotherapy (n=1233)	Vedolizumab and thiopurines (n=214)	Vedolizumab monotherapy (n=1141)	Vedolizumab and thiopurines (n=289)
Age, mean (SD), year	42.3 (14.3)	41.2 (12.7)	46.5 (17.2)	43.1 (14.5)	39.2 (13.6)	36.1 (12.0)
Sex						
Male	608 (41.3)	128 (39.3)	527 (42.7)	91 (42.5)	421 (36.9)	112 (38.8)
Female	863 (58.7)	198 (60.7)	706 (57.3)	123 (57.5)	720 (63.1)	177 (61.2)
Crohn's disease duration, mean (SD), year	-	-	-	-	9.9 (6.5)	9.4 (6.4)
Montreal phenotype						
B1	784 (53.3)	158 (48.5)	695 (56.4)	104 (48.6)	740 (64.9)	208 (72.0)
B2	348 (23.7)	85 (26.1)	288 (23.4)	50 (23.4)	220 (19.3)	55 (19.0)
B3	339 (23.0)	83 (25.5)	250 (20.3)	60 (28.0)	181 (15.9)	26 (9.0)
Perianal Crohn's disease	156 (10.6)	40 (12.3)	64 (5.2)	19 (8.9)	321 (28.1)	91 (31.5)
Crohn's disease complicated disease course						
More than 180 days before cohort entry	142 (9.7)	41 (12.6)	114 (9.2)	18 (8.4)	315 (27.6)	69 (23.9)
Surgery related to Crohn's disease						
More than 180 days before cohort entry	236 (16.0)	54 (16.6)	171 (13.9)	30 (14.0)	459 (40.2)	115 (39.8)
Number of prior anti-TNFs						
0	421 (28.6)	69 (21.2)	509 (41.3)	66 (30.8)	-	-
1	707 (48.1)	157 (48.2)	543 (44.0)	101 (47.2)	425 (37.2)	84 (29.1)
2	294 (20.0)	81 (24.8)	155 (12.6)	33 (15.4)	628 (55.0)	183 (63.3)
3	49 (3.3)	18 (5.5)	26 (2.1)	14 (6.5)	80 (7.0)	22 (7.6)
4	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	8 (0.7)	0 (0.0)
Anti-TNF within 180 days before cohort entry	678 (46.1)	172 (52.8)	488 (39.6)	110 (51.4)	801 (70.2)	233 (80.6)
Corticosteroids (oral)						
within 180 days before cohort entry	924 (62.8)	218 (66.9)	645 (52.3)	137 (64.0)	604 (52.9)	152 (52.6)
at cohort entry	443 (30.1)	99 (30.4)	326 (26.4)	70 (32.7)	314 (27.5)	99 (34.3)
Aminosalicylates (oral)	648 (44.1)	148 (45.4)	467 (37.9)	86 (40.2)	739 (64.8)	183 (63.3)
Opioids	643 (43.7)	132 (40.5)	412 (33.4)	88 (41.1)	176 (15.4)	33 (11.4)
Crohn's disease activity assessment †						
Hospitalization related to Crohn's disease	91 (6.2)	26 (8.0)	83 (6.7)	12 (5.6)	217 (19.0)	66 (22.8)
Abdominal imaging	495 (33.7)	114 (35.0)	475 (38.5)	90 (42.1)	471 (41.3)	136 (47.1)
Lower GI endoscopy	530 (36.0)	154 (47.2)	512 (41.5)	90 (42.1)	525 (46.0)	144 (49.8)
Upper GI endoscopy	186 (12.6)	47 (14.4)	187 (15.2)	27 (12.6)	166 (14.5)	50 (17.3)
CRP tests ordered, mean (SD)	0.97 (1.35)	1.30 (1.67)	1.46 (2.23)	1.76 (2.06)	3.12 (2.64)	3.84 (3.25)
Fecal pathogen tests ordered	230 (15.6)	61 (18.7)	247 (20.0)	46 (21.5)	133 (11.7)	43 (14.9)

Supplementary Table 3. Characteristics of study patients with Crohn's disease treated with vedolizumab monotherapy or vedolizumab and thiopurines, before propensity score-matching (continued)

	MarketScan		Optum		SNDS	
Variable	Vedolizumab monotherapy (n=1471)	Vedolizumab and thiopurines (n=326)	Vedolizumab monotherapy (n=1233)	Vedolizumab and thiopurines (n=214)	Vedolizumab monotherapy (n=1141)	Vedolizumab and thiopurines (n=289)
Comorbidities						
clostridioides difficile infection	33 (2.2)	5 (1.5)	28 (2.3)	3 (1.4)	37 (3.2)	6 (2.1)
Serious infection	26 (1.8)	6 (1.8)	21 (1.7)	4 (1.9)	16 (1.4)	7 (2.4)
Cardiovascular disease	113 (7.7)	16 (4.9)	142 (11.5)	23 (10.7)	120 (10.5)	22 (7.6)
Chronic kidney failure	38 (2.6)	4 (1.2)	54 (4.4)	11 (5.1)	30 (2.6)	5 (1.7)
Chronic liver disease	34 (2.3)	6 (1.8)	96 (7.8)	16 (7.5)	25 (2.2)	3 (1.0)
Chronic pulmonary disease	231 (15.7)	44 (13.5)	205 (16.6)	41 (19.2)	393 (34.4)	90 (31.1)
Venous thromboembolism	36 (2.4)	8 (2.5)	28 (2.3)	7 (3.3)	60 (5.3)	11 (3.8)
Diabetes	94 (6.4)	16 (4.9)	128 (10.4)	15 (7.0)	60 (5.3)	9 (3.1)
Healthcare use characteristics †						
Hospitalizations not related to Crohn's disease	124 (8.4)	20 (6.1)	95 (7.7)	21 (9.8)	108 (9.5)	26 (9.0)
Gastroenterologist visits, mean (SD)	4.63 (6.25)	5.40 (7.12)	5.72 (6.98)	6.70 (9.74)	3.74 (4.81)	3.61 (5.72)

Data are n (%) unless otherwise stated. † Assessed within 180 days before cohort entry

Supplementary Table 4. Characteristics of study patients with ulcerative colitis treated with vedolizumab monotherapy or vedolizumab and thiopurines, before propensity score-matching

	MarketScan		Optum		SNDS	
Variable	Vedolizumab monotherapy (n=1684)	Vedolizumab and thiopurines (n=445)	Vedolizumab monotherapy (n=1649)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=1172)	Vedolizumab and thiopurines (n=350)
Age, mean (SD), year	41.6 (14.5)	41.2 (13.6)	45.0 (17.0)	43.2 (15.6)	44.1 (15.9)	39.3 (13.8)
Sex						
Male	840 (49.9)	211 (47.4)	783 (47.5)	155 (47.7)	584 (49.8)	188 (53.7)
Female	844 (50.1)	234 (52.6)	866 (52.5)	170 (52.3)	588 (50.2)	162 (46.3)
Ulcerative colitis disease duration (years), mean (SD)	-	-	-	-	7.8 (5.8)	6.7 (5.2)
Number of prior anti-TNFs						
0	640 (38.0)	135 (30.3)	831 (50.4)	138 (42.5)	-	-
1	760 (45.1)	226 (50.8)	660 (40.0)	145 (44.6)	556 (47.4)	162 (46.3)
2	255 (15.1)	72 (16.2)	146 (8.9)	39 (12.0)	499 (42.6)	172 (49.1)
3	27 (1.6)	12 (2.7)	10 (0.6)	3 (0.9)	112 (9.6)	16 (4.6)
4	2 (0.1)	0 (0)	2 (0.1)	0 (0)	5 (0.4)	
Anti-TNF within 180 days before cohort entry	824 (48.9)	246 (55.3)	688 (41.7)	158 (48.6)	962 (82.1)	315 (90.0)
Aminosalicylates (oral) at cohort entry	563 (33.4)	170 (38.2)	553 (33.5)	119 (36.6)	352 (30.0)	95 (27.1)
Corticosteroids (oral)						
within 180 days before cohort entry	1234 (73.3)	345 (77.5)	1137 (69.0)	240 (73.8)	771 (65.8)	244 (69.7)
at cohort entry	702 (41.7)	193 (43.4)	652 (39.5)	134 (41.2)	440 (37.5)	156 (44.6)
Opioids	537 (31.9)	151 (33.9)	341 (20.7)	55 (16.9)	120 (10.2)	27 (7.7)
Ulcerative colitis activity assessment †						
Hospitalization related to ulcerative colitis	147 (8.7)	43 (9.7)	160 (9.7)	28 (8.6)	168 (14.3)	55 (15.7)
Abdominal imaging	233 (13.8)	77 (17.3)	364 (22.1)	54 (16.6)	173 (14.8)	69 (19.7)
Lower GI endoscopy	912 (54.2)	245 (55.1)	929 (56.3)	195 (60.0)	759 (64.8)	255 (72.9)
Upper GI endoscopy	127 (7.5)	21 (4.7)	128 (7.8)	17 (5.2)	100 (8.5)	34 (9.7)
CRP tests ordered, mean (SD)	1.03 (1.34)	1.44 (2.10)	1.60 (1.80)	1.60 (1.91)	3.59 (2.75)	4.27 (3.57)
Fecal pathogen tests ordered	563 (33.4)	182 (40.9)	666 (40.4)	133 (40.9)	297 (25.3)	97 (27.7)
Comorbidities						
clostridioides difficile infection	89 (5.3)	30 (6.7)	87 (5.3)	13 (4.0)	42 (3.6)	17 (4.9)
Serious infection	25 (1.5)	3 (0.7)	30 (1.8)	5 (1.5)	17 (1.5)	6 (1.7)
Cardiovascular disease	144 (8.6)	25 (5.6)	190 (11.5)	29 (8.9)	144 (12.3)	27 (7.7)
Chronic kidney failure	37 (2.2)	6 (1.3)	52 (3.2)	5 (1.5)	18 (1.5)	3 (0.9)
Chronic liver disease	26 (1.5)	2 (0.4)	106 (6.4)	17 (5.2)	26 (2.2)	7 (2.0)
Chronic pulmonary disease	227 (13.5)	52 (11.7)	230 (13.9)	38 (11.7)	341 (29.1)	74 (21.1)
Venous thromboembolism	40 (2.4)	6 (1.3)	46 (2.8)	15 (4.6)	48 (4.1)	10 (2.9)
Diabetes	117 (6.9)	38 (8.5)	173 (10.5)	32 (9.8)	108 (9.2)	27 (7.7)

Supplementary Table 4. Characteristics of study patients with ulcerative colitis treated with vedolizumab monotherapy or vedolizumab and thiopurines, before propensity score-matching (continued)

	MarketScan		Optum		SNDS	
Variable	Vedolizumab monotherapy (n=1684)	Vedolizumab and thiopurines (n=445)	Vedolizumab monotherapy (n=1649)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=1172)	Vedolizumab and thiopurines (n=350)
Healthcare use characteristics †						
Hospitalizations not related to ulcerative colitis	85 (5.0)	21 (4.7)	109 (6.6)	20 (6.2)	99 (8.4)	16 (4.6)
Gastroenterologist visits, mean (SD)	5.39 (6.61)	5.96 (7.81)	6.32 (7.19)	6.65 (7.89)	5.33 (6.26)	5.41 (6.86)

Data are n (%) unless otherwise stated. † Assessed within 180 days before cohort entry

Supplementary Table 5. Outcomes, propensity score-matched with a 1:1 fixed ratio

Crohn's disease	MarketScan		Optum		SNDS		Overall cohort	
	Vedolizumab monotherapy (n=325)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=211)	Vedolizumab and thiopurines (n=211)	Vedolizumab monotherapy (n=268)	Vedolizumab and thiopurines (n=268)	Vedolizumab monotherapy (n=804)	Vedolizumab and thiopurines (n=804)
Treatment failure	95 (29.2)	83 (25.5)	59 (28.0)	52 (24.6)	122 (45.5)	101 (37.7)	276 (34.3)	236 (29.4)
Hospitalisation or surgery related to CD	40 (12.3)	30 (9.2)	25 (11.8)	23 (10.9)	71 (26.5)	54 (20.1)	136 (16.9)	107 (13.3)
Switch to another biologics or tofacitinib	18 (5.5)	20 (6.2)	15 (7.1)	15 (7.1)	57 (21.3)	45 (16.8)	90 (11.2)	80 (10.0)
Corticosteroids exposure at week 26	47 (14.5)	47 (14.5)	27 (12.8)	22 (10.4)	37 (13.8)	30 (11.2)	111 (13.8)	99 (12.3)

Ulcerative colitis	MarketScan		Optum		SNDS		Overall cohort	
	Vedolizumab monotherapy (n=440)	Vedolizumab and thiopurines (n=440)	Vedolizumab monotherapy (n=325)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=323)	Vedolizumab and thiopurines (n=323)	Vedolizumab monotherapy (n=1088)	Vedolizumab and thiopurines (n=1088)
Treatment failure	101 (23.0)	96 (21.8)	72 (22.2)	58 (17.8)	90 (27.9)	82 (25.4)	263 (24.2)	236 (21.7)
Hospitalisation related to UC or colectomy	18 (4.1)	26 (5.9)	11 (3.4)	16 (4.9)	25 (7.7)	25 (7.7)	54 (5.0)	67 (6.2)
Switch to another biologics or tofacitinib	15 (3.4)	9 (2.0)	7 (2.2)	7 (2.2)	22 (6.8)	16 (5.0)	44 (4.0)	38 (3.5)
Corticosteroids exposure at week 16	74 (16.8)	74 (16.8)	58 (17.8)	46 (14.2)	61 (18.9)	52 (16.1)	193 (17.7)	172 (15.8)

Supplementary Table 6. Adverse events, propensity score-matched with a 1:1 fixed ratio

Crohn's disease	MarketScan		Optum		SNDS		Overall cohort	
	Vedolizumab monotherapy (n=325)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=211)	Vedolizumab and thiopurines (n=211)	Vedolizumab monotherapy (n=268)	Vedolizumab and thiopurines (n=268)	Vedolizumab monotherapy (n=804)	Vedolizumab and thiopurines (n=804)
Serious infection	12 (3.7)	6 (1.8)	2 (0.9)	4 (1.9)	2 (0.7)	2 (0.7)	16 (2.0)	12 (1.5)
Hospitalisation not related to CD	51 (15.7)	45 (13.8)	38 (18.0)	30 (14.2)	26 (9.7)	21 (7.8)	115 (14.3)	96 (11.9)

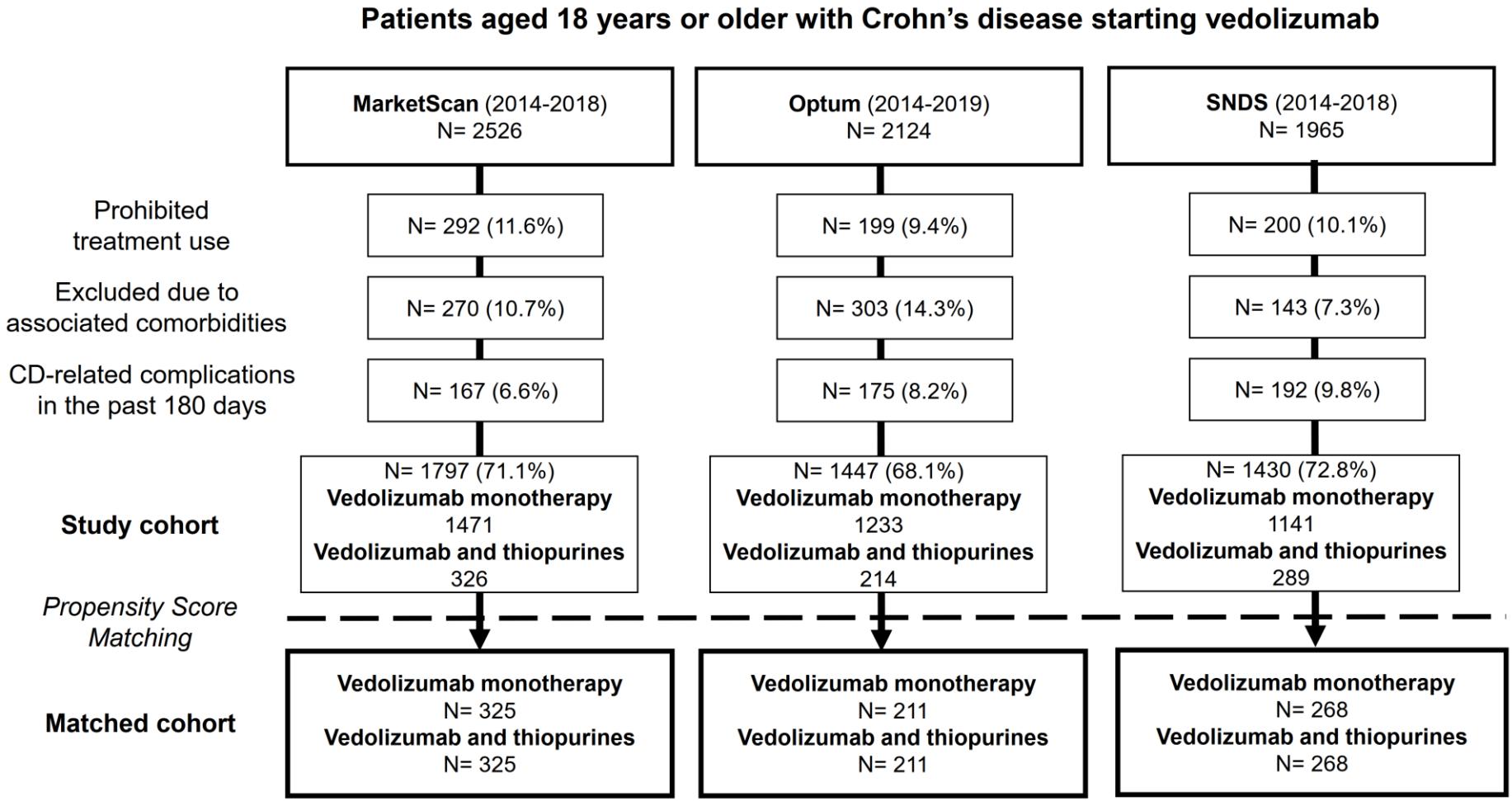
Ulcerative colitis	MarketScan		Optum		SNDS		Overall cohort	
	Vedolizumab monotherapy (n=440)	Vedolizumab and thiopurines (n=440)	Vedolizumab monotherapy (n=325)	Vedolizumab and thiopurines (n=325)	Vedolizumab monotherapy (n=323)	Vedolizumab and thiopurines (n=323)	Vedolizumab monotherapy (n=1088)	Vedolizumab and thiopurines (n=1088)
Serious infections	5 (1.1)	5 (1.1)	4 (1.2)	4 (1.2)	3 (0.9)	3 (0.9)	12 (1.1)	12 (1.1)
Hospitalisation not related to UC	31 (7.0)	35 (8.0)	22 (6.8)	30 (9.2)	16 (5.0)	12 (3.7)	69 (6.3)	77 (7.1)

Supplementary Table 7. Relative risk of treatment failure in patients treated with combination therapy versus vedolizumab monotherapy, sensitivity analyses

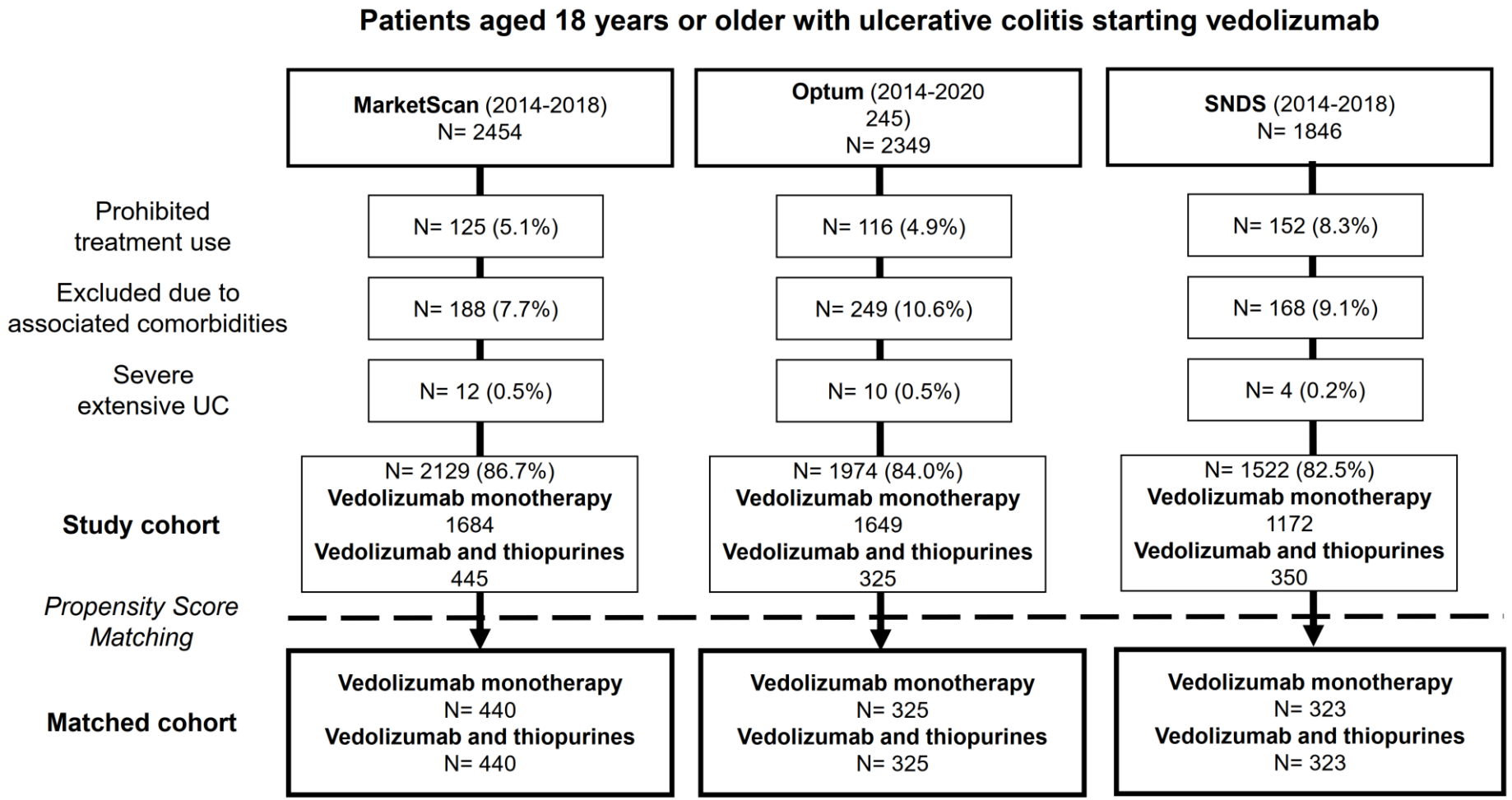
Crohn's disease	MarketScan	Optum	SNDS	Overall combined
Analyses				
Generalized linear model adjusted for variables included in the propensity score model and with absolute standardized differences > 0.1	0.89 (0.68-1.16)	1.01 (0.72-1.41)	0.91 (0.76-1.08)	0.92 (0.8-1.05)
Propensity score-matching with a 1:4 variable ratio	0.89 (0.69-1.15)	0.92 (0.67-1.27)	0.83 (0.68-1.01)	0.86 (0.75-1.00)
Exclusion of patients with an enrollment period of less than one year before cohort entry in the US databases	1.00 (0.75-1.33)	0.95 (0.66-1.38)	0.83 (0.68-1.01)	0.89 (0.77-1.04)

Ulcerative colitis	MarketScan	Optum	SNDS	Overall combined
Analyses				
Generalized linear model adjusted for variables included in the propensity score model and with absolute standardized differences > 0.1	0.95 (0.74-1.22)	0.79 (0.58-1.08)	0.91 (0.71-1.18)	0.89 (0.77-1.04)
Propensity score-matching with a 1:4 variable ratio	0.97 (0.75-1.26)	0.86 (0.62-1.19)	0.96 (0.77-1.19)	0.94 (0.81-1.09)
Exclusion of patients with an enrollment period of less than one year before cohort entry in the US databases	0.95 (0.73-1.24)	0.91 (0.65-1.28)	0.91 (0.71-1.18)	0.93 (0.79-1.09)
Extension of follow-up to week 26	0.99 (0.85-1.17)	0.80 (0.63-1.01)	1.03 (0.78-1.34)	0.94 (0.83-1.06)

Supplementary Figure 1. Study population flowchart, patients with Crohn's disease



Supplementary Figure 2. Study population flowchart, patients with ulcerative colitis



Supplementary Figure 3. Standardized differences before and after propensity score matching (Crohn's disease, MarketScan [A], Optum[B], and SNDS [C]; ulcerative colitis, MarketScan [D], Optum[E], and SNDS [F])