



Drug survival of anti-TNF agents compared with vedolizumab as a second-line biological treatment in inflammatory bowel disease: results from nationwide Swedish registers

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Funding information

This study was funded in part by Takeda Pharma AB, grant number IISR-2017-101937. The study design, collection, analysis and interpretation of data and drafting of manuscript were solely done by the authors without contribution from any of the funding organisations.

Summary

Background: Comparisons of second-line anti-tumour necrosis factor (TNF) agents and vedolizumab are sparse.

Aim: To evaluate the effectiveness of anti-TNF agents compared to vedolizumab as second-line biologics in inflammatory bowel disease (IBD).

Methods: A propensity score-matched cohort was created using Swedish nationwide registers. Patients with Crohn's disease or ulcerative colitis, exposed to first-line anti-TNF treatment, who initiated a second anti-TNF agent or vedolizumab in 2014-2016 (N = 1363) were included. The primary outcome was drug survival at 12 months. Secondly, we assessed survival without IBD-related hospitalisation, IBD-related surgery, antibiotics, or hospitalisation because of infection, and also corticosteroid exposure.

Results: After 1:1 propensity score matching, 400 patients (Crohn's disease, N = 198; ulcerative colitis, N = 202) remained. For Crohn's disease, drug survival was 73% in the vedolizumab group vs 74% in the anti-TNF group (difference: 1 percentage point; 95% confidence interval [CI]: -11-13; P = 0.87). Survival without IBD-related hospitalisation (82% vs 88%), surgery (82% vs 89%), antibiotics (65% vs 71%), hospitalisation due to infection (95% vs 88%) and corticosteroids (58% vs 48%) were not statistically significantly different between groups. For ulcerative colitis, drug survival was 69% in the vedolizumab group vs 62% in the anti-TNF group (difference: -7 percentage points; 95% CI: -20 to 6; P = 0.30). Vedolizumab-treated patients had lower survival without IBD-related hospitalisation (82% vs 93%, P = 0.02). Survival without colectomy (93% vs 97%), antibiotics (81% vs 70%), hospitalisation due to infection (92% vs 92%) and corticosteroids (58% vs 48%) were not statistically significantly different.

Conclusions: Based on Swedish clinical practice, the effectiveness and safety of second-line anti-TNF and vedolizumab at 12 months appeared largely similar.

Collaborators of the SWIBREG Study Group are listed in Appendix 1.

The Handling Editor for this article was Professor Richard Geary, and it was accepted for publication after full peer-review.

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1 | INTRODUCTION

The anti-tumour necrosis factor (TNF) agents infliximab,¹⁻⁴ adalimumab⁵⁻¹⁰ and golimumab¹¹⁻¹⁴ were the first biological agents to be approved for the treatment of moderate to severe Crohn's disease and ulcerative colitis, refractory or intolerant to conventional therapy. The efficacy and safety of these drugs have been demonstrated in numerous randomised controlled trials^{2-4,6-10,12-14} and observational studies.¹⁵⁻²⁰ Since 2014, the anti-integrin antibody vedolizumab has also been available as an alternative biological treatment of inflammatory bowel disease (IBD).²¹⁻²³ In many areas, treatment patterns and choice of first-line treatment are heavily influenced by the introduction of anti-TNF biosimilars and the cost savings that are associated with these drugs.²⁴ However, more than a third of patients do not respond to first-line anti-TNF therapy and 25%-40% of the patients who initially respond lose response over time or discontinue treatment because of intolerable side effects.²⁵⁻²⁷

Whether vedolizumab or an alternative anti-TNF agent should be used among patients who have discontinued first-line anti-TNF treatment is largely unknown. The VARSITY trial, representing the only randomised head-to-head comparison, was conducted on mostly anti-TNF naïve patients.²⁸ In addition, anti-TNF treatment was restricted to adalimumab and most patients treated in clinical practice would not have been eligible for the VARSITY trial, where inclusion was restricted to patients of certain ages, degrees of disease activity, comorbidity, prior and concurrent medications. Real-world studies comparing the effectiveness of an anti-TNF agent vs vedolizumab show conflicting data and some include a mixture of patients with different anti-TNF exposure, making the results difficult to interpret.²⁹⁻³⁴

These recent studies highlight that information on valuable clinical effectiveness measures can be obtained from real-world studies, but the lack of a randomised design may easily introduce bias due to confounding by indication. Drug survival rates are of particular interest, since they reflect a context-specific combination of effectiveness and safety. One way to avoid such channelling bias is to restrict the comparisons to second line-treatment where the initial channelling was to a different agent and to balance groups by propensity score matching. Therefore, we aimed to compare the effectiveness and safety of vedolizumab vs anti-TNF as second-line biological treatment in patients with IBD. Our primary measure of effectiveness was defined as drug survival and we used propensity score-matched analyses to account for potential confounding.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a population-based cohort study, based on data in routine clinical practice from nationwide registers in Sweden. Patients with IBD were identified using the International Classifications of

Disease (ICD) codes in the National Patient Register (NPR). The definition of IBD required a minimum of two inpatient or hospital outpatient care visits listing a diagnosis of IBD (Table S1) in the National Patient Register or at least one diagnosis of IBD in the Swedish National Quality Register for Inflammatory Bowel Disease (SWIBREG). This definition has a positive predictive value for IBD of 93% when National Patient Register data are used alone and 99% when combining data from the Swedish National Quality Register for Inflammatory Bowel Disease and the National Patient Register.³⁵ Different IBD diagnoses might be documented during a patient's medical history.³⁶ Patients who shifted between IBD diagnoses but only had one of the diagnoses in the 5 years preceding start of follow-up were classified according to their most recent diagnosis. Otherwise, we classified patients with a mix of codes as inflammatory bowel disease unclassified (IBD-U). However, patients who had a diagnostic or procedure code typical of Crohn's disease (Table S2) were classified as Crohn's disease. The IBD phenotype was categorised according to the Montreal classification (Table S3).³⁷

Patients with Crohn's disease or ulcerative colitis were included if they were exposed to an anti-TNF (infliximab, adalimumab or golimumab) as a first-line biological and commenced treatment with vedolizumab or an anti-TNF (infliximab, adalimumab or golimumab) as a second-line biological from 1 May 2014 to 31 December 2016. Medical treatment was recorded based on Anatomical Therapeutic Chemical (ATC) codes (Table S4). A minimum follow-up of 1 year was required, to allow comparisons with most clinical trial data. Patients exposed to certolizumab, natalizumab or ustekinumab as first- or second-line biological therapy were excluded. Similarly, those who stopped and restarted the same anti-TNF were excluded. Switching between a reference product and a biosimilar (same compound) was not considered discontinuation. All patients were followed from the commencement date of the second-line biological until emigration, death or end of follow-up on 31 December 2017.

2.2 | Data sources

The unique personal identification number, issued to all Swedish residents,³⁸ was used to link data from the following national registers:

The National Patient Register holds records of hospital admissions since 1964, with nationwide coverage since 1987, surgical outpatient procedures since 1997 and hospital outpatient physician visits from 2001 and onwards.³⁹ Surgical procedure codes for IBD in the National Patient Register were recently validated, revealing an overall positive predictive value of 97% (95% confidence interval [CI] = 94-99).⁴⁰ The register also contains information on infusions of biologicals administered in a hospital setting, although the coverage varies between different counties (in manuscript).

The Swedish Prescribed Drug Register contains data on prescribed drugs since 2005, with complete coverage for dispensed prescriptions in healthcare, since reporting to the register is mandatory and regulated by national laws.⁴¹ However, in-hospital use of drugs is captured to a lesser extent. Information on infusion biologicals was

supplemented with data from the Swedish National Quality Register for Inflammatory Bowel Disease, which currently includes >50 000 IBD patients in Sweden.⁴² The register holds information on clinical variables such as diagnosis, medication, reason for drug discontinuation and smoking status.^{42,43}

2.3 | Outcome measures

Baseline was defined as the date of initiation of the second-line biological drug. The primary objective was to examine the drug survival (as proxy for clinical effectiveness) at 12 months of vedolizumab compared to anti-TNFs when used as second-line biological, stratified by IBD subtype. A patient was considered having discontinued treatment if a date of discontinuation was recorded in the Swedish National Quality Register for Inflammatory Bowel Disease, if more than 3 months passed since the last infusion was recorded in National Patient Register or if more than 6 months passed since the last prescription was recorded in the Prescribed Drug Register.

Secondarily, we assessed effectiveness and safety at 12 months by measuring the survival without (a) hospital admission (because of IBD, IBD-related surgery or complications of IBD, as defined in Tables S1, S5 and S6), (b) IBD-related surgery (Table S5), (c) prescription of antibiotics (Table S7), as proxy for infection, and (d) hospital admission with infection as any diagnosis (Table S8), as proxy for severe infection. Furthermore, the cumulative steroid dose in prednisolone equivalents (Table S9) over the 12-month study period was assessed. The distribution of the cumulative corticosteroid dose was highly right skewed. Therefore, the doses were categorised into five groups: 0 mg, >0-1500 mg, >1500-3000 mg, >3000-4500 mg and >4500 mg. These categories approximately correspond to 0-4 episodes of corticosteroid treatment, since a typical course of corticosteroids used to treat an IBD flare in Sweden contains approximately 1500 mg of prednisolone equivalents. All secondary outcomes were compared between patients treated with vedolizumab vs patients treated with anti-TNF as second-line biological, stratified by IBD subtype.

As exploratory analyses, drug survival was assessed as a function of the first anti-TNF. Thus, four different switching strategies were compared: first infliximab then adalimumab, infliximab then vedolizumab, adalimumab then infliximab and adalimumab then vedolizumab. Switching strategies including golimumab were excluded, since the number of patients exposed to golimumab was too low to perform statistical analysis. Furthermore, drug survival of the second biological was assessed stratified by reason for discontinuation of first anti-TNF: lack of response or intolerance.

2.4 | Propensity score matching

Since patients were not randomly assigned to receive vedolizumab or anti-TNF treatment, propensity score matching was performed

to reduce the effect of treatment selection bias and simulate the effects of randomisation. Propensity scores (the conditional probabilities of receiving vedolizumab treatment given the observed covariates) were estimated using logistic regression models (one for Crohn's disease and one for ulcerative colitis) based on the potential confounders age, disease duration, sex, previous IBD-related surgery, concomitant corticosteroids, concomitant immunomodulator, smoking status, reason for terminating of first anti-TNF (lack of response, intolerance, other), type of first anti-TNF (infliximab, adalimumab, golimumab), disease extent (ulcerative colitis only), disease location (Crohn's disease only), disease behaviour (Crohn's disease only) and the presence of perianal disease (Crohn's disease only). One-to-one nearest neighbour matching without replacement was performed with a maximum caliper of 10% of the standard deviation of the estimated propensity scores. The resulting propensity score-matched pairs were used in subsequent analyses. Covariate balance was checked by comparing median and means of baseline characteristics between matched groups and plotting histograms of the propensity scores.

2.5 | Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) and differences by treatment group were tested with the Mann-Whitney U test. Categorical data are presented as frequencies and differences in the distributions by treatment group were assessed using Pearson Chi-square test or Fisher's exact test when appropriate. Kaplan-Meier curves were used to estimate survival curves of the different outcomes. Log-rank tests and complementary log-log transformation were used to compare survival data between groups. All tests were two-tailed and *P*-values of < 0.05 were considered statistically significant. Statistical analyses and data processing were performed in R version 3.6.1 (R Foundation for Statistical Computing) and SPSS version 22 (IBM Corp.).

2.6 | Ethical considerations

Ethical approval for this study was granted by the Regional Ethics Committee, Karolinska Institute, Stockholm, Sweden (2007/785-31/5; 2011/1509-32; 2015/0004-31; 2015/615-32).

3 | RESULTS

3.1 | Cohort of patients treated with a second-line biological

In total, 881 patients with Crohn's disease (Table 1) and 482 patients with ulcerative colitis (Table 2) were identified. After 1:1 propensity score matching, the cohort for analyses was restricted to 198

TABLE 1 Baseline demographics and clinical characteristics of patients with Crohn's disease

	Overall cohort (N = 881)			Propensity matched cohort (N = 198)		
	Anti-TNF N = 775	Vedolizumab N = 106	P-value ^a	Anti-TNF N = 99	Vedolizumab N = 99	P-value ^a
Male, N (%)	381 (49)	56 (53)	0.48	49 (50)	52 (53)	0.67
Disease duration in years, median (IQR)	9 (4-18)	10 (4-24)	0.15	10 (3-18)	10 (4-22)	0.33
Age in years, median (IQR)	37 (26-51)	47 (22-54)	<0.01 ^d	42 (27-55)	45 (32-54)	0.69
Smoking status, N (%)			<0.01 ^d			0.59
Smoker	64 (8)	7 (7)		3 (3)	7 (7)	
Never smoker	152 (20)	32 (30)		33 (33)	31 (31)	
Ex-smoker	80 (10)	24 (23)		21 (21)	18 (18)	
Data missing	479 (62)	43 (41)		42 (42)	43 (43)	
Behaviour, N (%)			0.37			0.66
Non-stricturing, non-penetrating (B1)	544 (70)	74 (70)		64 (65)	71 (72)	
Stricturing (B2)	89 (12)	16 (15)		14 (14)	13 (13)	
Penetrating (B3)	91 (12)	7 (7)		16 (16)	10 (10)	
Data missing	22 (3)	5 (5)		5 (5)	5 (5)	
Perianal disease, N (%)			0.18			0.55
Yes	186 (24)	17 (16)		22 (22)	16 (16)	
Data missing	17 (2)	3 (3)		3 (3)	3 (3)	
Location, N (%)			0.17			0.94
Ileal (L1)	228 (29)	37 (35)		38 (38)	34 (34)	
Colonic (L2)	298 (39)	43 (41)		37 (37)	41 (41)	
Ileocolonic (L3)	227 (29)	21 (20)		19 (19)	19 (19)	
Data missing	22 (3)	5 (5)		5 (5)	5 (5)	
Concomitant medication, N (%)						
Corticosteroids	229 (30)	45 (43)	0.01 ^d	49 (50)	40 (40)	0.20
Immunomodulators ^b	204 (26)	20 (19)	0.10	17 (17)	20 (20)	0.58
Previous IBD-related surgery, N (%)	383 (49)	48 (45)	0.42	42 (42)	45 (46)	0.67
Reason for termination of first anti-TNF, N (%)			0.07			0.70
Lack of response	217 (28)	36 (34)		40 (40)	35 (35)	
Intolerance	195 (25)	33 (31)		29 (29)	29 (29)	
Other reason ^c	363 (47)	37 (35)		30 (30)	35 (35)	
Type of first anti-TNF, N (%)			<0.001 ^d			0.67
Infliximab	574 (74)	40 (38)		43 (43)	40 (40)	
Adalimumab	190 (25)	66 (62)		56 (57)	59 (60)	
Golimumab	11 (1)	0 (0)		0 (0)	0 (0)	
Propensity score, median (IQR)	0.1 (0.0-0.1)	0.2 (0.1-0.4)	<0.001 ^d	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.98

Abbreviations: anti-TNF, anti-tumour necrosis factor; IBD, inflammatory bowel disease; IQR, interquartile range.

^aAnti-TNF vs vedolizumab, Mann-Whitney U test or chi-squared test used when appropriate.

^bIncluding azathioprine, 6-mercaptopurine and methotrexate.

^cIncluding patient's preferences, physician's decision, pregnancy, death or unknown.

^dSignificant P-values.

patients with Crohn's disease and 202 patients with ulcerative colitis. No statistically significant differences in the observed covariates between vedolizumab and anti-TNF-treated patients remained

after matching (Tables 1 and 2). Switching patterns and histograms of propensity scores before and after matching are available in the supplements (Figures S1-S3).

TABLE 2 Baseline demographics and clinical characteristics of patients with ulcerative colitis

	Overall cohort (N = 482)			Propensity matched cohort (N = 202)		
	Anti-TNF N = 372	Vedolizumab N = 110	P-value ^a	Anti-TNF N = 101	Vedolizumab N = 101	P-value ^a
Male, N (%)	215 (58)	72 (65.5)	0.15	62 (61)	64 (63)	0.77
Disease duration in years, median (IQR)	7 (3-14)	5 (2-12)	0.02 ^d	7 (3-14)	6 (2-12)	0.21
Age in years, median (IQR)	40 (21-52)	35 (25-48)	0.04 ^d	34 (26-44)	35 (25-48)	0.58
Smoking status, N (%)			<0.01 ^d			0.95
Smoker	10 (3)	2 (2)		3 (3)	2 (2)	
Never smoker	82 (22)	42 (38)		33 (33)	35 (35)	
Ex-smoker	52 (14)	21 (19)		21 (21)	19 (19)	
Missing	228 (61)	45 (41)		44 (44)	45 (45)	
Disease extent, N (%)			0.02 ^d			0.67
Proctitis (E1)	16 (4)	2 (2)		5 (5)	2 (2)	
Left sided (E2)	64 (17)	20 (18)		15 (15)	18 (18)	
Extensive (E3)	237 (64)	83 (76)		76 (75)	76 (75)	
Unspecified (EX)	55 (15)	5 (5)		5 (5)	5 (5)	
Concomitant medication, N (%)						
Corticosteroids	156 (42)	60 (55)	0.02 ^d	48 (48)	52 (52)	0.57
Immunomodulators ^b	121 (33)	35 (32)	0.89	30 (30)	30 (30)	1.00
Previous colectomy, N (%)	18 (5)	6 (6)	0.79	6 (6)	6 (6)	1.00
Reason for termination of first anti-TNF, N (%)			<0.001 ^d			1.00
Lack of response	136 (37)	66 (60)		58 (57)	58 (57)	
Intolerance	60 (16)	17 (16)		16 (16)	16 (16)	
Other reason ^c	176 (47)	27 (25)		27 (27)	27 (27)	
Type of first anti-TNF, N (%)			0.16			0.34
Infliximab	265 (71)	68 (62)		64 (63)	62 (61)	
Adalimumab	94 (25)	36 (33)		30 (30)	36 (36)	
Golimumab	13 (4)	6 (6)		7 (7)	3 (3)	
Propensity score, median (IQR)	0.2 (0.1-0.3)	0.3 (0.2-0.4)	<0.001 ^d	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.91

Abbreviations: anti-TNF, anti-tumour necrosis factor; IQR, interquartile range.

^aAnti-TNF vs vedolizumab, Mann-Whitney U test or chi-squared test used when appropriate.

^bIncluding azathioprine, 6-mercaptopurine and methotrexate.

^cIncluding patient's preferences, physician's decision, pregnancy, death or unknown.

^dSignificant P-values.

3.2 | Outcomes in patients with Crohn's disease

3.2.1 | Effectiveness

In Crohn's disease, drug survival at 12 months was 73% in the vedolizumab group, compared to 74% in the anti-TNF group (difference: 1 percentage points; 95% CI: -11 to 13; $P = 0.87$; Figure 1A, Table 3). Among vedolizumab-treated patients, 27/99 (27%) terminated treatment due to lack of response ($N = 11$), intolerance

($N = 6$) or other reasons ($N = 10$). Correspondingly, 26/99 (26%) of the anti-TNF-treated patients stopped treatment due to lack of response ($N = 9$), intolerance ($N = 5$) or other reasons ($N = 12$). Drug survival at 14 weeks was 86% in the vedolizumab group and 92% in the anti-TNF group.

The survival without IBD-related hospital admission (82% vs 88%, $P = 0.25$) and IBD-related surgery (82% vs 89%, $P = 0.17$) did not differ significantly between the groups (Figure 2, Table 3). Proportion of patients who were exposed to corticosteroids during

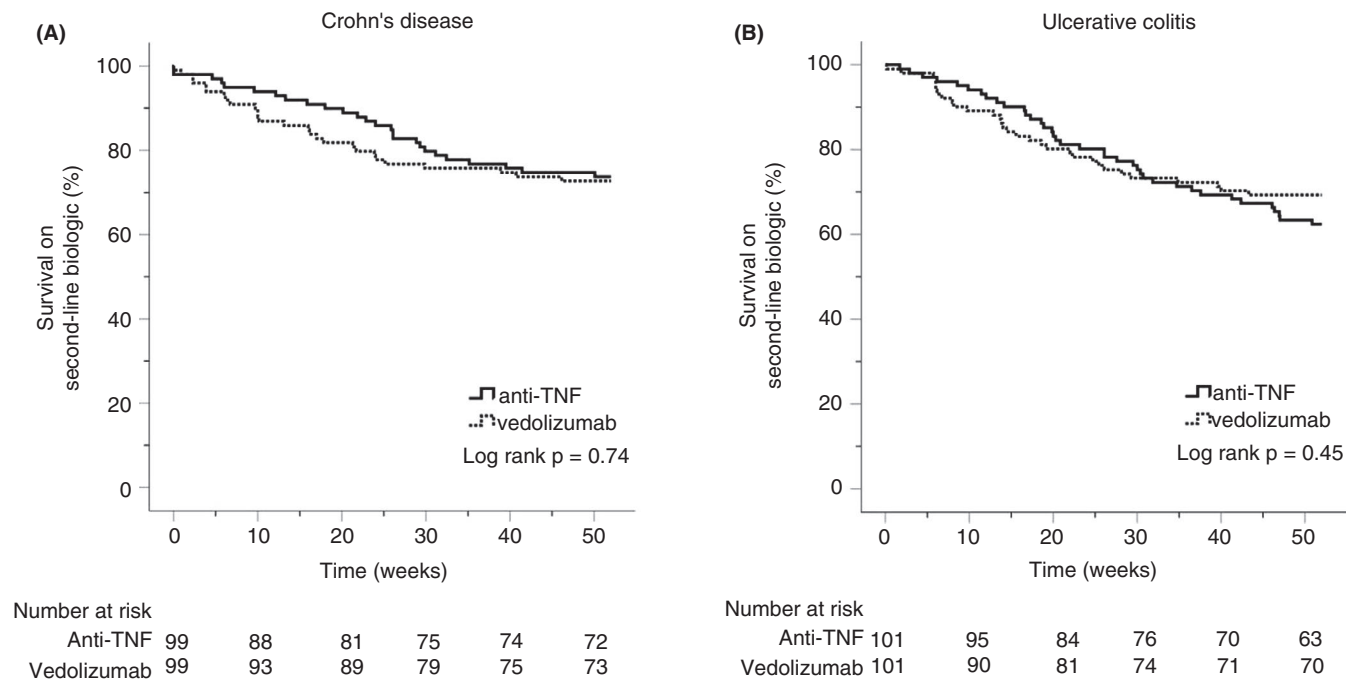


FIGURE 1 Kaplan-Meier curves illustrating survival on second-line biological of propensity score-matched cohort of patients with (A) Crohn's disease and (B) ulcerative colitis

	Anti-TNF N = 99	Vedolizumab N = 99	Difference in survival ^a	P- value
Drug survival on second-line biological	74	73	1 (-11 to 13)	0.87
Number of events	26	27		
Survival without IBD-related hospital admission	88	82	6 (-4 to 16)	0.24
Number of events	12	18		
Survival without IBD-related surgery	89	82	7 (-3 to 17)	0.17
Number of events	11	18		
Survival without prescription of antibiotics	71	65	6 (-7 to 19)	0.36
Number of events	29	35		
Survival without hospital admission due to infection	88	95	-7 (-15 to 1)	0.09
Number of events	12	5		

Abbreviations: anti-TNF, anti-tumour necrosis factor; IBD, inflammatory bowel disease.

^aDifference in survival in percentage points between anti-TNF and vedolizumab with 95% confidence interval.

follow-up was 52% in the vedolizumab group and 51% in the anti-TNF group ($P = 0.89$, Figure 3A).

3.2.2 | Safety

Survival without prescription of antibiotics (65% vs 71%, $P = 0.33$) and hospital admission with infection as any diagnosis (95% vs 88%, $P = 0.08$) did not differ significantly between the groups (Figure 2, Table 3).

TABLE 3 Survival and number of events at 12 months in patients with Crohn's disease

3.2.3 | Effectiveness of different switching strategies

Drug survival at 12 months was 81% for patients switching from infliximab to adalimumab ($N = 42$), 75% for patients switching from infliximab to vedolizumab ($N = 40$), 71% for patients switching from adalimumab to infliximab ($N = 45$) and 71% for patients switching from adalimumab to vedolizumab ($N = 59$). No significant differences between different switching strategies were found ($P = 0.64$).

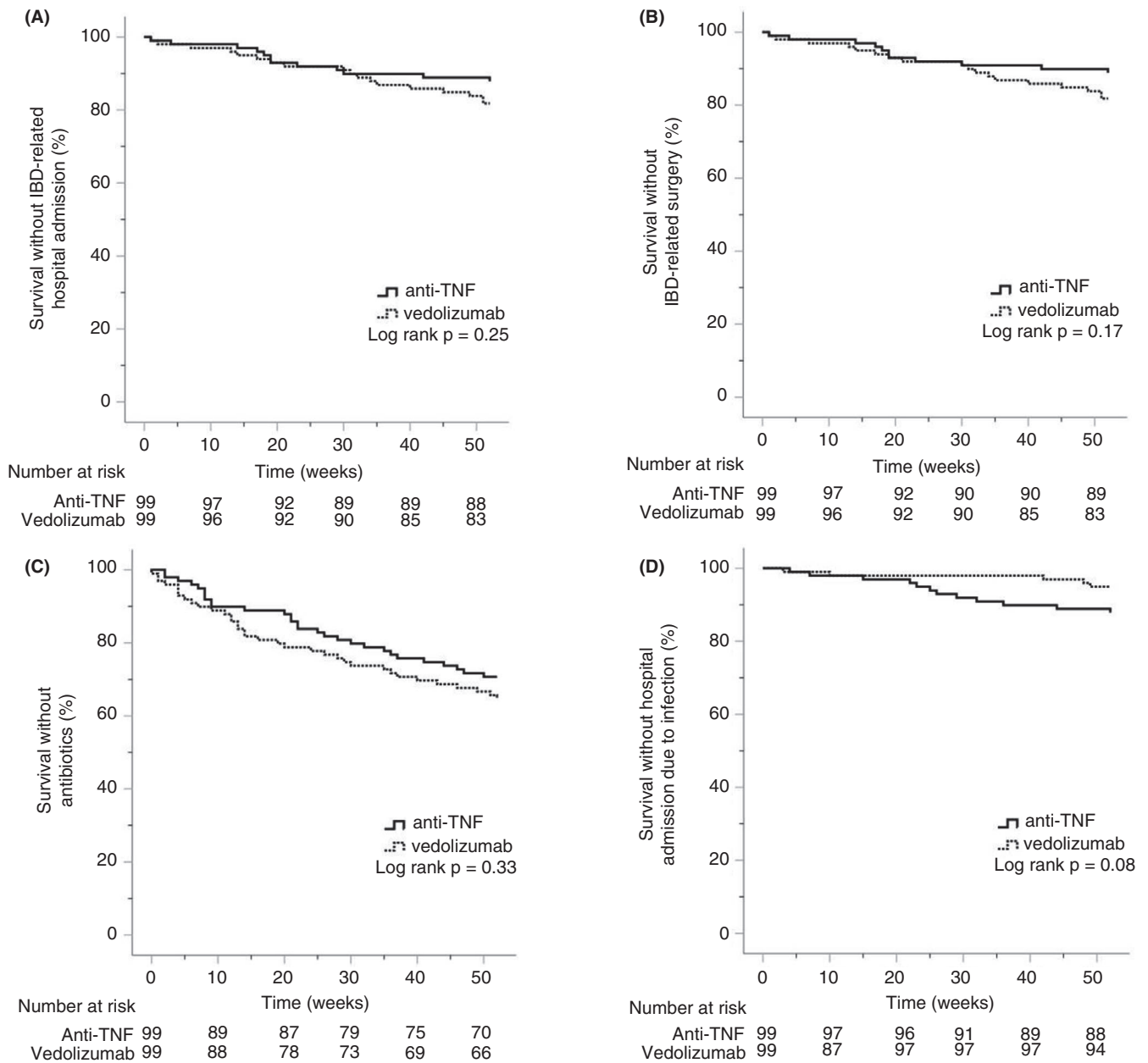


FIGURE 2 Kaplan-Meier curves in propensity score-matched cohort of patients with Crohn's disease illustrating survival without (A) inflammatory bowel disease-related hospital admission, (B) inflammatory bowel disease-related surgery, (C) antibiotics, (D) hospital admission due to infection

3.2.4 | Effectiveness of second-line biological by reason for discontinuation of first anti-TNF

When stratified by reason for discontinuation of first anti-TNF, drug survival at 12 months among patients who stopped their first anti-TNF due to lack of response (vedolizumab N = 35, anti-TNF N = 40) did not significantly differ between the groups (69% vs 65%, P = 0.96). Likewise, no differences in drug survival were observed among patients (vedolizumab N = 29, anti-TNF N = 29) who discontinued their first anti-TNF because of intolerance (76% vs 76%, P = 0.90).

3.3 | Outcomes in patients with ulcerative colitis

3.3.1 | Effectiveness

In ulcerative colitis, drug survival at 12 months was 69% in the vedolizumab group compared to 62% in anti-TNF group (difference: -7 percentage points; 95% CI: -20 to 6; P = 0.30; Figure 1B, Table 4). Of the patients treated with vedolizumab, 31/101 (31%) terminated treatment due to lack of response (N = 19), intolerance (N = 7) or other reasons (N = 5). Correspondingly, 38/101 (38%) of the anti-TNF-treated patients stopped treatment due to lack of response (N = 14), intolerance (N = 8) or other reasons (N = 16). Drug survival

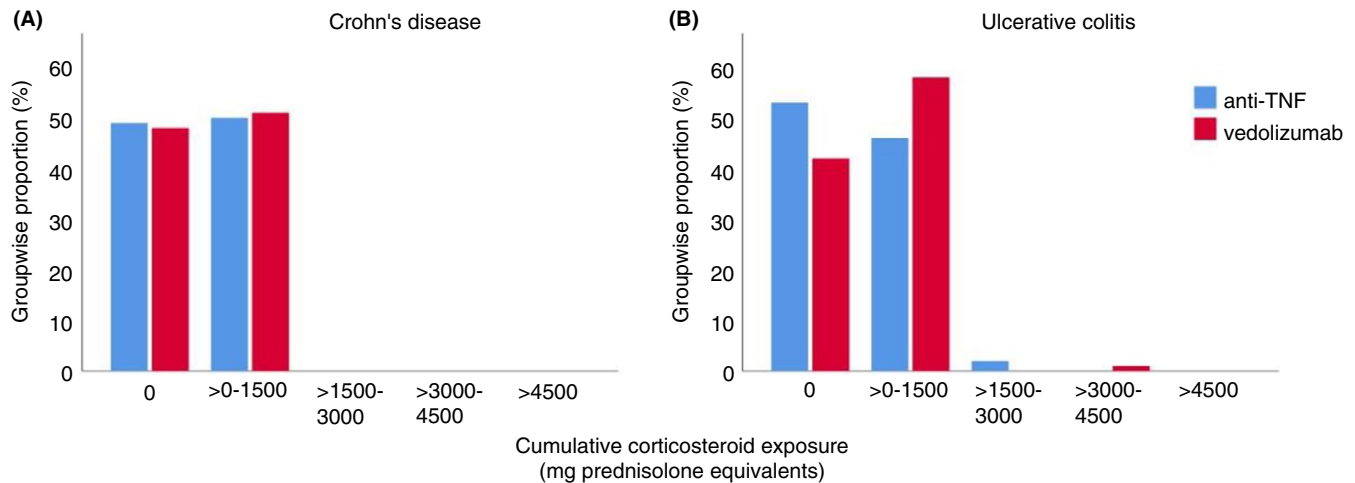


FIGURE 3 Cumulative corticosteroid exposure (mg prednisolone equivalents) at 12 months in patients with (A) Crohn's disease and (B) ulcerative colitis

	Anti-TNF N = 101	Vedolizumab N = 101	Difference in survival ^a	P- value
Drug survival on second-line biological	62	69	-7 (-20 to 6)	0.30
Number of events	38	31		
Survival without IBD-related hospital admission	93	82	11 (2-20)	0.02 ^b
Number of events	7	18		
Survival without colectomy	97	93	4 (-2 to 10)	0.21
Number of events	3	7		
Survival without prescription of antibiotics	70	81	-11 (-23 to 1)	0.07
Number of events	30	19		
Survival without hospital admission due to infection	92	92	0 (-7 to 7)	1
Number of events	8	8		

TABLE 4 Survival and number of events at 12 months in patients with ulcerative colitis

Abbreviations: anti-TNF, anti-tumour necrosis factor; IBD, inflammatory bowel disease.

^aDifference in survival percentage points between anti-TNF and vedolizumab with 95% confidence interval.

^bSignificant *P*-values.

at 14 weeks was 85% in the vedolizumab group and 91% in the anti-TNF group.

The survival without IBD-related hospital admission was lower in the vedolizumab group (ie they were more hospitalised) compared to the anti-TNF group (82% vs 93%, $P = 0.02$, Figure 4A, Table 4). Survival without colectomy did not differ significantly between the groups (93% vs 97%, $P = 0.19$, Figure 4B, Table 4). Proportion of patients who were exposed to any corticosteroids during follow-up was 58% in the vedolizumab group and 48% in the anti-TNF group ($P = 0.13$, Figure 3B).

3.3.2 | Safety

Survival without prescription of antibiotics (81% vs 70%, $P = 0.08$) and hospital admission with infection as any diagnosis (92% vs 92%, $P = 0.97$) did not differ significantly between the groups (Figure 4, Table 4).

3.3.3 | Effectiveness of different switching strategies

Drug survival rate at 12 months was 62% for patients switching from infliximab to adalimumab ($N = 58$), 68% for patients switching from infliximab to vedolizumab ($N = 62$), 67% for patients switching from adalimumab to infliximab ($N = 24$) and 75% for patients switching from adalimumab to vedolizumab ($N = 36$). No significant differences between different switching strategies were found ($P = 0.75$).

3.3.4 | Effectiveness of second-line biological by reason for discontinuation of first anti-TNF

When stratified by reason for discontinuation of first anti-TNF, drug survival at 12 months among patients who stopped their first

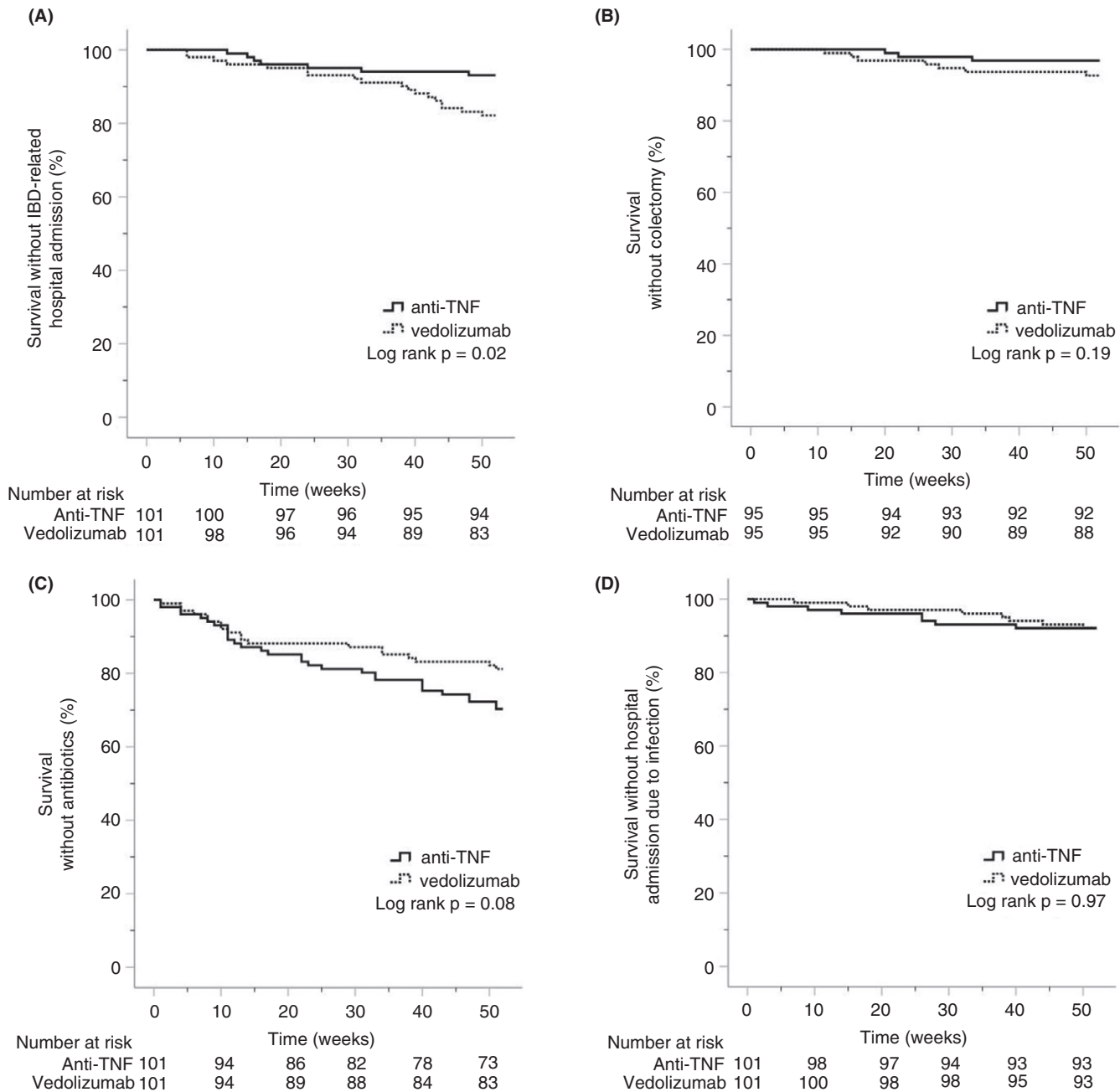


FIGURE 4 Kaplan-Meier curves in propensity score-matched cohort of patients with ulcerative colitis illustrating survival without (A) inflammatory bowel disease-related hospital admission (B) colectomy, (C) antibiotics, (D) hospital admission due to infection

anti-TNF due to lack of response (vedolizumab $N = 58$, anti-TNF $N = 58$) did not differ statistically significantly between the groups (67% vs 59%, $P = 0.43$). Likewise, no statistically significant differences in drug survival were observed among patients (vedolizumab $N = 16$, anti-TNF $N = 16$) who discontinued their first anti-TNF because of intolerance (50% vs 56%, $P = 0.56$).

4 | DISCUSSION

In this large national register-based propensity score-matched cohort of patients with IBD, we did not find evidence of notable

differences in drug survival nor safety profile between vedolizumab and anti-TNF when used as second-line treatment. Our findings are consistent with results from the recent head-to-head VARSITY trial, where no difference in clinical remission, endoscopic improvement or corticosteroid-free clinical remission was observed between second-line treatment with vedolizumab and adalimumab, among patients with ulcerative colitis.²⁸ Our findings indicate that the results from this trial are applicable to a broader population of patients with ulcerative colitis and not only those who were eligible for inclusion in the trial as well as to patients with Crohn's disease.

Even though numerous studies have demonstrated that biological agents can reverse the inflammation in IBD, a recent large

retrospective real-world study from the United States shows that more than half of patients with IBD discontinue treatment with their initial biological within the first 12 months.⁴⁴ Information on which biological agent to use as second-line treatment after initial anti-TNF failure is sparse and previous observational studies comparing the effectiveness of a second anti-TNF agent vs vedolizumab are limited by small sample size or study design.²⁹⁻³⁴

In the overall cohort, the VARSITY trial demonstrated a superior effect of vedolizumab compared to adalimumab in terms of clinical and endoscopic remission rates. These results are supported by a preliminary observational report, yet presented as abstracts only. Higher 12-month cumulative rates of clinical remission (54% vs 37%) and endoscopic healing (50% vs 42%) were observed for vedolizumab compared to anti-TNF-treated patients with ulcerative colitis in the US-based VICTORY consortium when propensity score matching was performed.⁴⁵ However, the same consortium observed no significant differences in serious infections, clinical remission, steroid-free clinical remission or endoscopic remission when Crohn's disease patients treated with vedolizumab were compared with patients who were treated with an anti-TNF agent.⁴⁶ Comparisons with these observational reports are challenging because they represent a mix of first- and second-line treatments.^{45,46} In contrast, Favale et al examined the effectiveness of vedolizumab vs adalimumab as second-line treatment among 161 Italian patients with ulcerative colitis who had failed infliximab treatment.³³ Consistent with our findings, there was no statistically significant difference between the two groups. However, among patients with a secondary loss of response to first-line infliximab, vedolizumab was associated with significantly lower treatment failure rate (22%) compared to adalimumab (48%) as well as increased discontinuation-free survival (319 vs 251 median days). In contrast to this study, we could not adjust our analyses by primary non-response and secondary loss of response, since this information was not available in the national registers. The results from the Italian study may potentially indicate that vedolizumab could be a better option for ulcerative colitis patients with secondary failure to infliximab. However, some patients had been followed for less than 52 weeks and the results are susceptible to channelling bias. Another observational study compared effectiveness of vedolizumab vs infliximab in 225 patients with ulcerative colitis who previously failed subcutaneous anti-TNF treatment.³⁴ In contrast to our findings, the authors observed a higher drug survival in the overall cohort at 1 year when vedolizumab-treated patients (80%) were compared with infliximab treated (50%). However, the infliximab-treated patients had a higher partial Mayo score at baseline and more frequently initiated treatment during hospital admission.

Vedolizumab has been associated with a beneficial safety profile, including less risk of infections compared to anti-TNF agents.²⁸ In this study, we were not able to demonstrate any statistically significant difference in survival rates without hospital admission due to infection and prescription of antibiotics. In addition to the comparative analyses of effectiveness and safety, we tried to assess an

optimal switching strategy, but once more without observing any significant differences between the different switching patterns. However, the study was not primarily designed to address this endpoint and the absence of significant differences may reflect low statistical power rather than true-negative findings since only 24-68 patients remained within each group.

Interestingly, the survival without IBD-related hospital admission was lower in the vedolizumab group compared to the anti-TNF group (82% vs 93%). The reason for this finding is unknown, but the difference may potentially be explained by more frequent dose escalation of anti-TNF agents. In contrast, Adar et al reported a higher rate of IBD-related hospital admissions during first year of treatment among elderly IBD patients who received an anti-TNF agent (20%) vs vedolizumab (13%), but this difference was not significant on multi-variable analysis.³⁰

Our study has several strengths and limitations linked to its design and the use of data from nationwide registers. Even though it is important to generate information on real-world effectiveness and safety, the study is limited by its non-randomised design. However, by including patients on second-line biological therapy only, we were able to limit the influence of channelling bias (ie patients starting vedolizumab were recruited from a pool of patients who initially were channelled to treatment with infliximab or adalimumab, and vice versa). In addition, access to a large sample size with information on important confounders allowed the use of propensity score matching. We also restricted our analysis to the period when all drugs were available on the market, which otherwise is likely to influence drug survival. The study design allowed inclusion of all patients with IBD in Sweden, which minimises selection bias and increases the generalisability. The unique personal identification numbers allowed us to follow-up patients regardless of residential area, unless a patient emigrated or died, and resulted in minimal loss to follow-up.

Although propensity score matching was used to reduce bias in causal estimates due to observed differences between the vedolizumab and anti-TNF-treated patients, unmeasured confounders may still exist. The loss of patients in the matching process influenced the precision of the comparative estimates. To assess clinical effectiveness, we used drug survival. This simple indirect approach to assess the clinical effectiveness assumes that a patient continues treatment as long as it reduces disease activity and prevents flares.^{47,48} This assumption is most likely correct for biological treatments, since these medications are approved for maintenance treatment and used to prevent disease progression. However, the high drug survival rates after switch to a second anti-TNF agent observed in this study indicate that this measure may also be influenced by the number of alternative treatment options. The fact that drug survival at 12 months after switch to a second anti-TNF agent was numerically higher in Crohn's disease (74%) than in ulcerative colitis (62%) further supports the assumption that physicians and patients become increasingly hesitant to terminate an ongoing treatment when few alternatives remain. This since colectomy often is perceived as a better solution for patients with ulcerative colitis than for patients with Crohn's disease. The

lack of information on therapeutic drug monitoring (TDM), dose escalation, biomarkers and endoscopic activity represents additional limitations of the study. Especially, the lack of data on drug concentrations and possible anti-drug antibodies at termination of the first anti-TNF agent is an important limitation of the study. This since these laboratory measures may have influenced treatment decision, including the use of anti-TNF or vedolizumab as second-line biologics, and potentially also treatment outcomes. Access to therapeutic drug monitoring may also have varied across Sweden and differed between university hospitals and regional hospitals. Furthermore, effectiveness beyond the first year of treatment was not evaluated since follow-up was limited to 12 months. The study period was predefined by the protocol and was selected to allow comparisons with most clinical trial data and avoid incomplete follow-up. However, a recent study by Roblin et al showed that patients with immune-mediated loss of response to anti-TNF treatment favoured from combination therapy with azathioprine after a switch to a second anti-TNF agent, but this effect was only seen after 12 months.⁴⁹ This important result may indicate that a longer follow-up could have influenced our results and points to the importance of extended follow-up periods in future real-world studies.

In conclusion, the treatment outcomes observed among patients with IBD in Swedish clinical practice indicate a largely equal effectiveness and safety profile of vedolizumab compared with anti-TNF agents, when these drugs are used as second-line treatment. Other factors such as time to onset of action, cost-effectiveness, route of administration, patient preference, therapeutic drug monitoring and potential difference in clinical effectiveness beyond 12 months must be taken into account in clinical decision-making.

ACKNOWLEDGEMENTS

Declaration of personal interests: SR has served as a speaker for Takeda and has received research funding from the research committee in Region Örebro County and the Regional Agreement on Medical Training and Clinical Research between Region Örebro County and Örebro University: ALF. CE has served as a speaker, a consultant and an advisory board member for Takeda, Janssen Cilag, Pfizer, Abbvie, and has received research funding from the Regional Agreement on Medical Training and Clinical Research between Region Örebro County and Örebro University: ALF. OO has served as a speaker, a consultant and an advisory board member for Janssen, Ferring, Pfizer and Takeda, and has received research funding from the Swedish Medical Society, The Young Scholar Award from the Strategic Research Area Epidemiology program at Karolinska Institutet and the Regional Agreement on Medical Training and Clinical Research between Stockholm County Council and Karolinska Institutet: ALF. JH has served as a speaker, a consultant and an advisory board member for Abbvie, Celgene, Celltrion, Ferring, Hospira, Janssen, Medivir, MSD, Olink Proteomics, Pfizer, Prometheus Laboratories Inc, RenapharmaVifor, Sandoz, Shire, Takeda, Thermo Fisher and Tillotts Pharma. JH has received research funding from Janssen, MSD and Takeda. MS and SM.

AUTHORSHIP

Guarantor of the article: JH.

Author contributions: MS and OO involved in data acquisition. SR and MS involved in data analysis and creating figures and tables. SR and JH drafted the article. All authors substantially contributed to the study design, method, interpretation of data and revising manuscript critically for important intellectual. All authors approved the final version of the article, including the authorship list.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Rundquist S, Sachs MC, Eriksson C, Olén O, Montgomery S, Halfvarson J; The SWIBREG Study Group. Drug survival of anti-TNF agents compared with vedolizumab as a second-line biological treatment in inflammatory bowel disease: results from nationwide Swedish registers. *Aliment Pharmacol Ther.* 2021;53:471–483. <https://doi.org/10.1111/apt.16193>

APPENDIX 1

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