First-line anti-TNF agents, ustekinumab and vedolizumab perform similarly in Crohn' disease, but not in ulcerative colitis

Eva Supovec[a], Jurij Hanžel[a,b], Gregor Novak[a,b], Damjan Manevski[c], Borut Štabuc[a,b] and David Drobne[a,b]

Background Real-word comparisons between first-line biologicals in inflammatory bowel disease (IBD) are scarce.
Aims The aim of this study is to compare drug persistence and patient reported outcome-2 (PRO-2) remission rates of first-line biological classes [anti-tumor necrosis factor (TNF) agents vs anti-integrin vedolizumab vs IL-12/23 inhibitor ustekinumab] in real life cohort.
Methods Individual level data of 946 adults (588 Crohn's disease and 358 ulcerative colitis) were retrieved from UR-CARE IBD platform. Adjusted drug survival curves using a pooled logistic model and PRO-2 remission rates for each class of biologicals were calculated and compared.
Results In Crohn's disease, no differences in drug survival were observed for anti-TNF agents vs vedolizumab vs ustekinumab as estimated survival with 95% confidence intervals were 0.81 (0.77–0.84) vs 0.89 (0.82–0.96) vs 0.88 (0.79–0.97) at year 1 and 0.52 (0.46–0.58) vs 0.58 (0.37–0.78) vs 0.58 (0.39–0.77) at year 4. In ulcerative colitis, however, anti-TNF agents had shorter drug survival than vedolizumab with estimated drug survival with 95% confidence intervals 0.60 (0.52–0.67) vs 0.76 (0.67–0.84) at year 1 and 0.37 (0.30–0.44) vs 0.50 (0.36–0.64) at year 4. No differences in PRO-2 remission rates were observed between drug classes in Crohn's disease ($P = 0.95$), but more patients enjoyed PRO-2 remission in ulcerative colitis treated with anti-TNF agents compared to vedolizumab (94.8 vs 78.9%, $P = 0.002$).
Conclusion Our real-world data suggest similar drug persistence and efficacy of first-line treatments with anti-TNF agents, vedolizumab and ustekinumab in Crohn's disease. In ulcerative colitis, however, drug persistence was higher for vedolizumab compared to anti-TNF agents, but on the cost of lower PRO-2 remission rates. Eur J Gastroenterol Hepatol 37: 557–564

Introduction

Inflammatory bowel disease (IBD), encompassing conditions such as Crohn's disease and ulcerative colitis, is a chronic, progressive, and recurrent inflammatory disease of the gastrointestinal tract, the incidence of which continues to rise [1]. Left untreated, IBD leads to cumulative intestinal damage, complications, and disability [2]. To reduce inflammation and prevent structural damage, effective and durable therapeutic options are needed.

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[a]Faculty of Medicine, University of Ljubljana, [b]Department of Gastroenterology, University Medical Centre Ljubljana and [c]Faculty of Medicine, Institute for Biostatistics and Medical Informatics, University of Ljubljana, Ljubljana, Slovenia

Correspondence to David Drobne, MD, PhD, Department of Gastroenterology, University Medical Centre Ljubljana, Japljeva 2, 1000 Ljubljana, Slovenia
Tel: +386 1 522 1552; e-mail: david.drobne@gmail.com

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Fortunately, several new treatments became available in the past years, including biologic agents such as anti-tumor necrosis factor agents (anti-TNF agents) inhibitors (e.g. adalimumab, infliximab, and golimumab), anti-integrin antibodies (e.g. vedolizumab), and anti-IL 12/23 antibody (ustekinumab) [3]. The increasing availability of biological agents opens an opportunity for sequencing. When selecting the most optimal therapy, data from head-to-head trials are most informative. However, only two head-to-head trials are available in IBD, namely the Varsity trial in ulcerative colitis (vedolizumab vs adalimumab) [4] and the SEAVUE study in Crohn's disease (ustekinumab vs adalimumab) [5]. The choice of biological agents is, therefore, often based on comparisons to placebo from registration clinical trials, cost, drug availability, theoretical advantages/disadvantages, and physician's experience [6].

Real-world data have been increasingly used to provide comparative data between biological agents [6–9] and guide physicians in decision-making on the most suitable first-line biologic. A commonly used measure in real-world setting is treatment persistence, which describes the proportion of patients continuing a biological agent. Treatment persistence is a surrogate marker of ongoing treatment efficacy, absence of significant adverse events, and physician and patient willingness to continue with the treatment [6].

The aim of this study was to assess efficacy of biological agents in a real-world cohort of biologically naïve IBD patients. We compared the persistence (drug survival)

and disease control [patient reported outcome-2 (PRO-2) remission] of different biological agents (anti-TNF agents vs vedolizumab vs ustekinumab) used first-line in Crohn's disease and ulcerative colitis patients.

Materials and methods

Data source and extraction

In this study we analyzed the outcome (drug survival and clinical remission) of first-line biological therapy started in patients with IBD. This was a cohort study of patients treated at the tertiary referral University Medical Centre in Ljubljana, Slovenia. We included all actively followed patients in our IBD unit, that is, those who had at least one follow-up visit between October 2021 and August 2022. This included all patients treated with biologicals in this period, but also those who were treated with biologicals before this visit and might have discontinued this by the time of respective follow-up visit. Individual level patient data was obtained from hospital electronic medical records which are linked with Slovenian IBD registry UR-CARE, which operates under the European Crohn's and Colitis Organisation [10]. Active utilization of UR-CARE Registry started in our center in 2019. Since then data on patients treated with biologicals were collected prospectively at each patient's visit, either by physician at consultation or by IBD nurse at scheduled visit for infusion of biologicals. At each of these visits data on biologicals used in each patient were recorded (ongoing treatment, switches). At these visits also data on disease activity (among other data) were recorded using questionnaires from the UR-CARE Registry. Thus most patient data were entered into the registry in a prospective fashion (demographics, disease extension, disease activity, deaths, drug initiation, drug discontinuation). However, some data were entered retrospectively for events that occurred before 2019 as the UR CARE registry was only started after this date. Examples of retrospectively entered data are drug initiation/discontinuation before 2019, and extraintestinal manifestations that occurred in past and similar. Data lock for this analysis and export were performed on 1 August 2022.

Patients

Using the above-described criteria we identified 1075 IBD patients who received at least one dose of biological drug in our IBD unit. We excluded 29 patients with diagnosis of IBD unclassified. Furthermore, due to the fact that in some age subgroups only certain therapies were used (e.g. in older patients anti-TNF agents were not used – thus comparisons would not be possible with vedolizumab or ustekinumab), we focused on the age groups in which all therapies were available – this was 18–75 years of age for Crohn's disease and 18–73 years for ulcerative colitis. Additionally, since only few patients received ustekinumab as first-line treatment in ulcerative colitis we excluded also these patients. The final analysis dataset was thus composed of 945 IBD patients, 587 with Crohn's disease and 358 with ulcerative colitis (Fig. 1).

Study outcomes

Drug survival calculation

Drug survival time was calculated for a first-line biological that the patient received. Starting and stopping dates

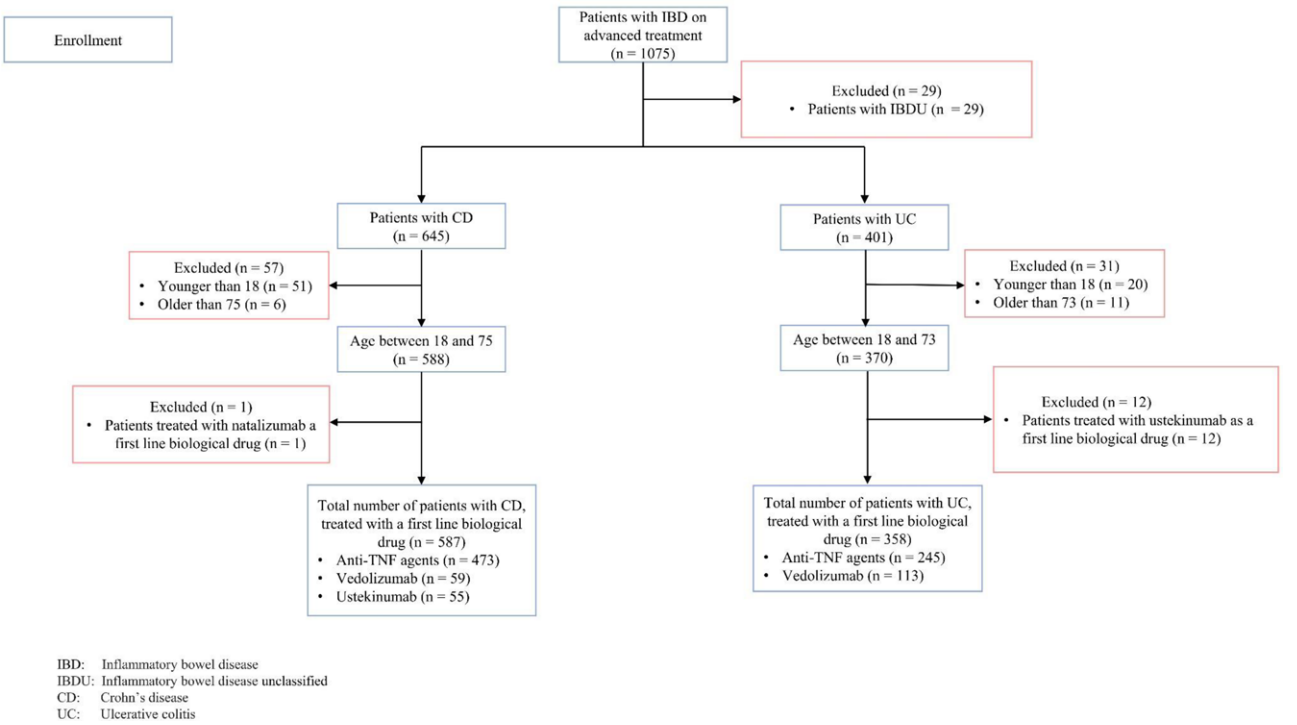

Fig. 1. Flowchart of included patients.

were obtained from the registry. These dates were entered prospectively when occurring after implementation of the registry in our IBD unit in 2019, but retrospectively based on patients' electronic data files when occurring before 2019. For prospectively entered biological treatments periods, the reason for discontinuation of therapy was known (loss of efficacy or a side effect), but not for retrospectively entered patients since the exact reason for discontinuation of the drug was difficult to assess from retrospective files in some cases. Patients who were still being treated with first-line biological at the time of data extraction (1 August 1 2022) were censored at this time point. Patients continuing first-line biological at the end of follow-up were censored. All other patients, who stopped the drug for loss of response or side effect, were coded as having an event in survival analyses.

Disease activity assessment

Since we also aimed to assess disease control of patients who were still actively treated with a first-line biological at the end of follow-up (i.e. of those who were censored at data extraction) we exported data of clinical activity recorded at the last visit of these patients from the UR CARE registry. Data on disease activity were prospectively collected in our outpatient unit with the help of standardized forms that are integrated in the UR CARE platform under section 'Follow-up & Laboratory Tests' as described above (ulcerative colitis: Supplementary Figure 1, Supplemental digital content 1, *http://links.lww.com/EJGH/B122* and Crohn's disease: Supplementary Figure 2, Supplemental digital content 1, *http://links.lww.com/EJGH/B122*). Disease activity was assessed at any clinical encounter, either at outpatient visit with physician or at visit infusion of biological with IBD nurse).

In ulcerative colitis rectal bleeding score (RBS) and stool frequency score (SFS) were assessed. RBS was scored from 0 to 3 (0, no blood seen; 1, streaks of blood with stool less than half of the time; 2, obvious blood with stool most of the time; 3, blood alone passes) and SFS was scored from 0 to 3 (0, normal number of stools for patient; 1, 1–2 stools per day more than normal; 2, 3–4 stools per day more than normal; 3, ≥5 stools than normal). In Crohn's disease abdominal pain score (APS) and number of daily liquid stools was assessed. APS was scored from 0 to 3 (0 – none, 1 – mild, 2 – moderate, 3 – severe). For all clinical scores the patients were asked to give an estimation of the last few days before the respective visit. The value entered into the registry was always the rounded natural number (i.e. no decimal values were possible). In the analyses, PRO-2 remission was defined in ulcerative colitis as RBS = 0 and SFS ≤ 1 and in Crohn's disease as APS ≤1 and number of liquid daily stools ≤1.5. Even though Physician Global Assessment score is included in the UR-CARE registry's questionnaire, we did not include it in the PRO-2 remission calculation due to its subjective nature.

Statistical analysis

Data were exported from UR-CARE to Microsoft Excel software (Version 2307 Build 16626.20134; Microsoft Corporation, Redmond, Washington, USA) and was arranged for statistical analysis. Then we calculated drug survival curves for first-line biologicals with the aim of investigating whether there were differences in drug survival for studied biologicals in Crohn's disease (anti-TNF agents vs vedolizumab vs ustekinumab) and ulcerative colitis (anti-TNF agents vs vedolizumab). The survival curves were adjusted for baseline covariates [gender, start of biological treatment before year 2019 vs after year 2019 (i.e. period <2019 vs period ≥2019), phenotype, disease duration, age], follow-up time, medication, and the following interactions: follow-up time and medication, period and medication. The adjusted survival curves were calculated as suggested by Hernan using a pooled logistic model for modeling the event probability [11]. Based on this model, the event probability was calculated for every individual for all therapies. The adjusted survival curves were obtained by averaging the probabilities across all patients. The confidence intervals (CIs) were obtained using 100 bootstrap replications. Additionally, we fitted Cox proportional hazard models for ulcerative colitis and Crohn's disease (hazard ratio). The included covariates in ulcerative colitis model were sex (female/male), biological therapy class (anti-TNF agents/vedolizumab), start of biological therapy (period <2019 vs period ≥2019), biological therapy class-start of biological therapy interaction, disease location (extensive colitis/proctitis/left-sided colitis), disease duration (in years), and age (in years). In the Crohn's disease model we used the same covariates [of note in Crohn's disease three biological classes were included (anti-TNF agents/vedolizumab/ustekinumab) and phenotypes were defined differently (isolated ileal/ileocolonic/colonic)]. Approximately 3% of all patients had missing disease location in the data. Data imputation of disease location was performed using multiple imputation (MICE) with respect to diagnosis, biologic type, gender, age, disease duration, period, and follow-up. We calculated proportion of patients in PRO-2 remission and median PRO-2 scores in each treatment arm (anti-TNF agents vs vedolizumab vs ustekinumab) for Crohn's disease and (anti-TNF agents vs vedolizumab) for ulcerative colitis and assessed results with Chi-square/Mann–Whitney *U* test as appropriate. Reported *P*-values are nominal, and value <0.05 were considered statistically significant. The analysis was performed in the R programming package version 4.3.1. Additional data plotting was done in Microsoft Excel software (Version 2307 Build 16626.20134) and Inkscape (Version 1.3.0.0; Inkscape Team, open source graphic software, https://inkscape.org/).

Results

Patients' characteristics

The final cohort for the analysis consisted of 945 adult patients with IBD (587 with Crohn's disease, 358 with ulcerative colitis) (for details about excluded patients see Fig. 1 – patient flow). Patient demographic data are summarized in Table 1.

In Crohn's disease, 473 (80.4%) patients were treated with anti-TNF agents (201 with infliximab, 272 with adalimumab), 59 (10.1%) vedolizumab and 55 (9.4%) patients with ustekinumab. In ulcerative colitis, 245 (68.4%) patients were treated with anti-TNF agents (152 with infliximab, 41 with adalimumab, 52 with golimumab) and 113 (31.6%) patients with vedolizumab.

Table 1. Patient demographics and characteristics

	Crohn's disease				Ulcerative colitis		
	Anti-TNF agents	Vedolizumab	Ustekinumab		Anti-TNF agents	Vedolizumab	Ustekinumab
N	473	59	55	*N*	245	113	/
Female, *n* (%)	214 (45.2)	28 (47.5)	23 (41.8)	Female, *n* (%)	129 (52.7)	57 (50.4)	
Median age, years [IQR]	37.7 [28.2–49]	55.9 [47.6–66.3]	56.9 [46.1–62.6]	Median age, years [IQR]	36.9[28–48]	46.7[34.5–61.5]	
Median disease duration, years [IQR]	7.4 [2.7–14.2]	10.2 [4.2–21.2]	11.5 [4–23.7]	Median disease duration, years [IQR]	4.4[1.7–9.8]	8.0[3.7–13]	
Disease location				Disease location			
Isolated ileal, *n* (%)	142 (30.0)	10 (16.9)	21 (38.2)	Proctitis, *n* (%)	7 (2.9)	6 (5.3)	
Colonic, *n* (%)	105 (22.2)	26 (44.1)	9 (16.4)	Left-sided colitis, *n* (%)	87 (35.5)	42 (37.2)	
Ileocolonic, *n* (%)	217 (45.9)	21 (35.6)	24 (43.6)	Extensive colitis, *n* (%)	141 (57.6)	62 (54.9)	
Period of start of first-line biological							
Until year 2019 (period <2019), *n* (%)	334 (70.6)	16 (27.1)	21 (38.2)	Until year 2019 (period <2019), *n* (%)	165 (67.3)	18 (15.9)	

IQR, interquartile range; TNF, tumor necrosis factor.

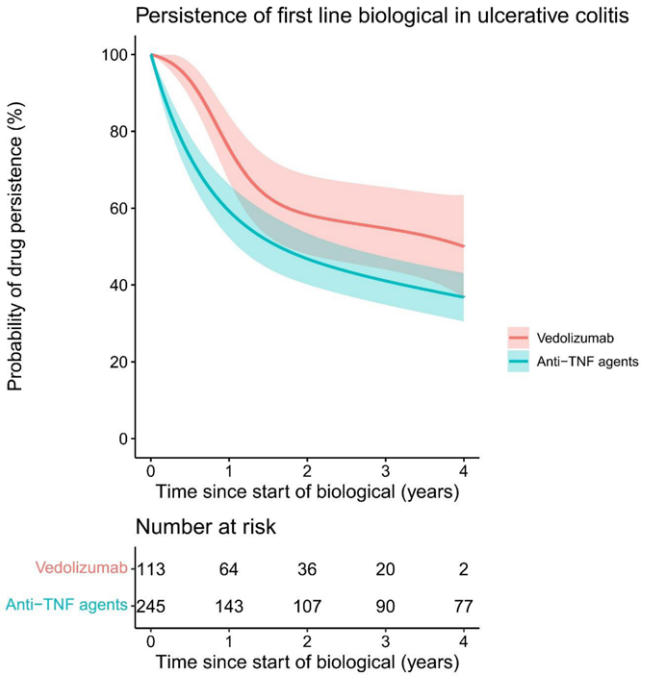

Fig. 2. Adjusted survival curves for ulcerative colitis with the corresponding 95% confidence intervals.

In Crohn's disease, patients treated with vedolizumab or ustekinumab were generally older and had longer median disease duration than patients treated with anti-TNF agents. Isolated ileal disease was twice as common in patients treated with anti-TNF agents as in those treated with vedolizumab or ustekinumab. Similarly, patients with ulcerative colitis treated with vedolizumab also had longer median disease duration than those treated with anti-TNF agents. However, their median age and disease location were comparable.

Drug survival and disease control by therapeutic class

We focused on drug survival during the first 4 years of treatment initiation as vedolizumab and ustekinumab-treated patients had shorter follow-up due to its latter introduction into clinical practice. Additionally, more than half of patients treated with anti-TNF agents discontinued these within 4 years of start. For these reasons patients were censored at 4 years.

Drug survival by therapeutic class

Adjusted survival curves for ulcerative colitis and Crohn's disease are shown in Figs. 2 and 3, while predictors of drug survival identified with Cox regression are summarized in Table 2.

Ulcerative colitis

In ulcerative colitis (Fig. 2), vedolizumab had longer drug survival that anti-TNF agents during the entire treatment period. During the first year of treatment both drug survival curves decreased swiftly and reached survival probabilities of 0.60 (95% CI: 0.52–0.67) and 0.76 (95% CI: 0.67–0.84) for anti-TNF agents and vedolizumab, respectively. Slower rate of drug survival decrease was observed after the first year of treatment. At the end of the observed period, at 4 years, anti-TNF agents still had shorter drug survival than vedolizumab, 0.37 (95% CI: 0.30–0.44) vs 0.50 (95% CI: 0.36–0.64), respectively. However, the CIs overlapped after the first year. Within anti-TNF agents drug survival was comparable for infliximab and adalimumab, but shorter for golimumab (Supplementary Figure 3, Supplemental digital content 1, *http://links.lww.com/EJGH/B122*).

Cox regression model (Table 2) suggested that drug survival was similar until 2019 for anti-TNF agents and vedolizumab (*P*-value = 0.63). However, after year 2019, vedolizumab had better drug survival than anti-TNF agents [hazard ratio and 95% CI: 0.24 (0.10–0.54)]. Furthermore, anti-TNF agents had worse drug survival after year 2019 [hazard ratio and 95% CI: 1.85 (1.25–2.72)]. The remaining covariates were not statistically significant in the model.

Crohn's disease

In Crohn's disease, drug survival was similar for anti-TNF agents, vedolizumab, and ustekinumab during the observed period. The estimated drug survivals were 0.81 (95% CI: 0.77–0.84), 0.89 (95% CI: 0.82–0.96), and 0.88 (95% CI: 0.79–0.97) at year 1 and 0.52 (95% CI: 0.46–0.58), 0.58 (95% CI: 0.37–0.78), and 0.58 (95% CI: 0.39–0.77) at year 4 for anti-TNF agents, vedolizumab, and

ustekinumab, respectively. Anti-TNF agents had shorter drug survival than vedolizumab and ustekinumab, but the corresponding CIs strongly overlap. Among the two anti-TNF agents, namely infliximab and adalimumab, no differences in drug survival were observed (Supplementary Figure 4, Supplemental digital content 1, *http://links.lww.com/EJGH/B122*).

Cox regression (Table 2, first column) suggested longer drug survival for females compared with males [hazard ratio with 95% CI: 0.62 (0.47–0.82)]. Also, patients with isolated ileal disease enjoyed longer drug survival than those with ileocolonic and colonic disease [hazard ratio with 95% CI: 1.37 (0.98–1.89) and 1.58 (1.08–2.30), respectively]. The remaining covariates were not statistically significant in the model.

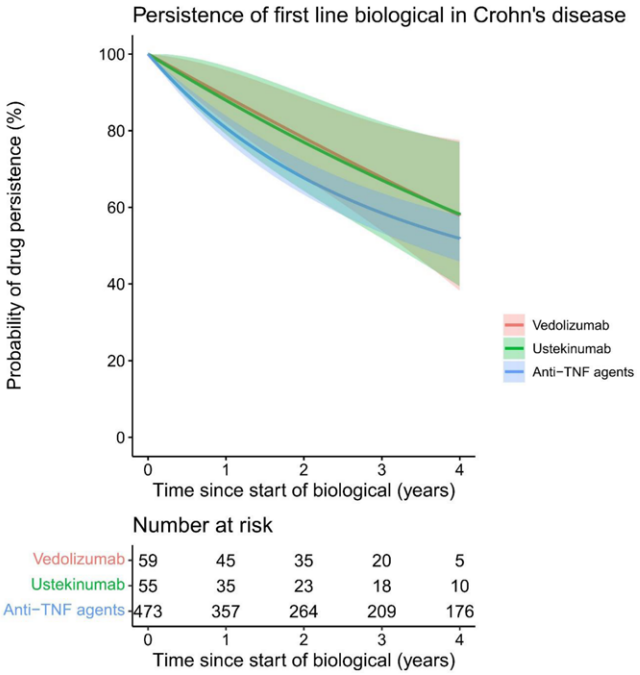

Fig. 3. Adjusted survival curves for Crohn's disease with the corresponding 95% confidence intervals.

Disease control by therapeutic class

At the end of follow-up, 302/587 (51.4%) patients with Crohn's disease and 173/358 (48.3%) patients with ulcerative colitis were still receiving first-line therapy. For the great majority of these patients [Crohn's disease: 295/302 patients (97.7%); ulcerative colitis: 172/173 patients (99.4%)] data on disease control at the last patient visit (PRO-2 score) were available in the registry close to data lock.

Most patients with ulcerative colitis were in clinical remission at the end of the follow up. However, proportion of patients in PRO-2 remission was higher in patients treated with anti-TNF agents than in those treated with vedolizumab (94.8 vs 78.9%, $P = 0.002$). We observed this for both items of PRO-2 score, for RBS and SFS (Fig. 4). Number of patients with SFS ≤ 1 was 96/96 (100%) and 68/76 (89.5%) in patients treated with anti-TNF agents and vedolizumab, respectively ($P = 0.0012$). RBS 0 was recorded in 91/96 (94.8%) and 63/76 (82.9%) of patients treated with anti-TNF agents and vedolizumab, respectively ($P = 0.011$).

In Crohn's disease, we did not observe statistically significant differences in clinical remission rates between different therapeutic classes ($P = 0.95$). No significant differences in SFS between therapeutic classes were observed ($P = 0.98$). However, mean APS was higher in patients treated with vedolizumab ($P = 0.03$) than in those treated with anti-TNF agents and ustekinumab (Fig. 5).

Discussion

The expanding therapeutic armamentarium for IBD in conjunction with a paucity of head-to-head trials complicates first-line biologic treatment selection. In this large single center cohort study based on the UR-CARE registry,

Table 2. Cox regression analysis for identifying factors associated with drug survival: hazard ratios and 95% confidence intervals (CI)

Crohn's disease			Ulcerative colitis		
	Hazard ratio with 95% confidence intervals	*P*-value		Hazard ratio with 95% confidence intervals	*P*-value
Sex, male[a]	0.62 (0.47–0.82)	<0.001	Sex, male[a]	0.88 (0.64–1.21)	0.44
Medication, vedolizumab[b]	0.91 (0.41–2.00)	0.82	Medication, vedolizumab[b]	1.17 (0.62–2.16)	0.63
Medication, ustekinumab[b]	1.03 (0.51–2.05)	0.94	/	/	/
Period ≥2019[c]	1.46 (1.04–2.04)	0.03	Period ≥2019[c]	1.85 (1.25–2.72)	<0.001
Medication, vedolizumab Period ≥2019[c]	0.60 (0.21–1.64)	0.32	Medication, vedolizumab Period ≥2019[c]	0.24 (0.10–0.54)	<0.001
Medication, ustekinumab Period ≥2019[c]	0.41 (0.11–1.39)	0.15	/	/	/
Phenotype, ileocolonic[d]	1.37 (0.98–1.89)	0.06	Phenotype, proctitis[e]	0.61 (0.22–1.68)	0.34
Phenotype, colonic[d]	1.58 (1.08–2.30)	0.02	Phenotype, left-sided colitis[e]	1.09 (0.78–1.51)	0.62
Disease duration	1.01 (0.99–1.03)	0.34	Disease duration	1.01 (0.98–1.03)	0.69
Age	0.99 (0.98–1.01)	0.20	Age	1.01 (0.99–1.02)	0.24

[a]vs female (used as reference).
[b]vs anti-TNF agents (used as reference).
[c]vs period <2019 (used as reference).
[d]vs isolated ileal (used as reference).
[e]vs extensive colitis (used as reference).

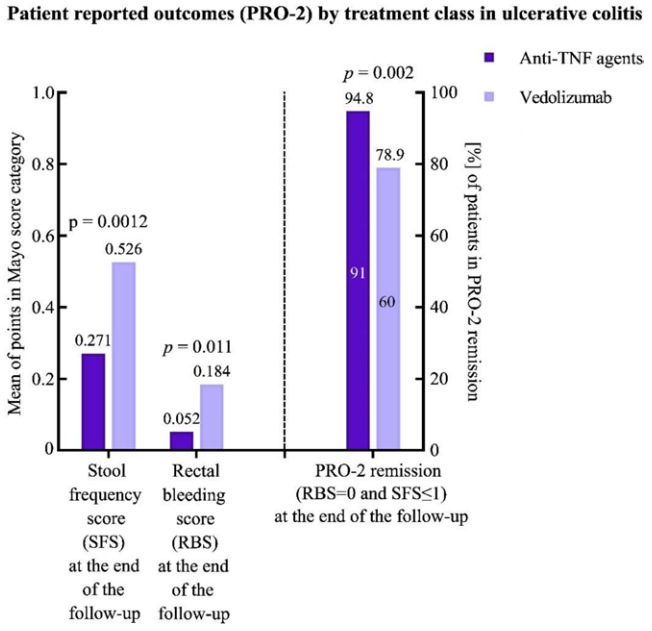

Fig. 4. Mean scores in PRO-2 remission categories in patients with ulcerative colitis.

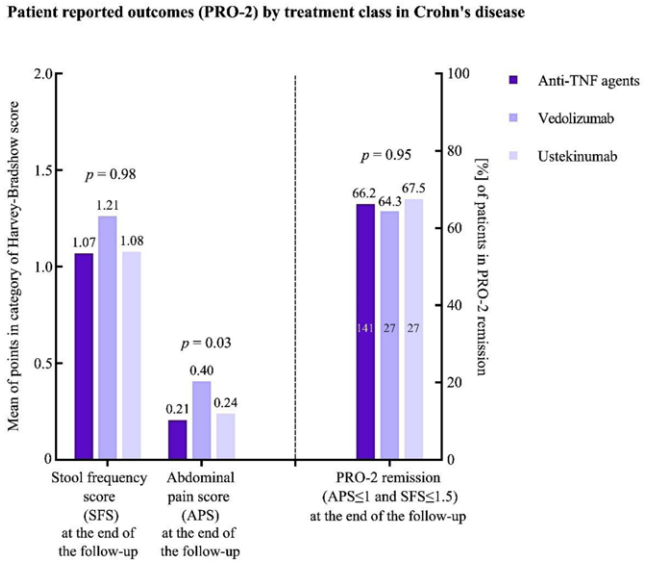

Fig. 5. Mean scores in PRO-2 remission categories in patients with Crohn's disease.

we found that first-line vedolizumab was associated with longer treatment persistence compared to anti-TNF agents in ulcerative colitis. All classes of biologics performed similarly in Crohn's disease. Neither disease extent nor duration impacted persistence of the first-line agent and differences between classes of biologics in ulcerative colitis persisted after adjustment through rigorous statistical modeling.

In ulcerative colitis, first-line vedolizumab was superior to anti-TNF agents (76 vs 60% persistence after 12 months). Within anti-TNF agents, infliximab and adalimumab had comparable treatment persistence, whereas persistence with golimumab was lower. Our findings are concordant with several cohort studies [8,9,12–14]. In a single-center retrospective study mimicking the randomized VARSITY trial comparing adalimumab to vedolizumab in 109 patients with ulcerative colitis [4], vedolizumab was superior both in terms of endoscopic outcomes (endoscopic improvement: 51 vs 26% at week 52) and treatment persistence (median treatment duration of 66 vs 33 weeks) [12]. Similar persistence at 1 year (78.6 vs 66.1%) was observed in an Australian cohort study with 420 ulcerative colitis patients [13]. Similar was replicated in a large UK IBD BioResource cohort [14] and in a recent meta-analysis [15].

While differences in persistence remained apparent throughout the duration of follow-up in our study, CIs began to overlap in the latter half of follow-up, owing to a decrease in patient numbers. Larger cohort studies demonstrated superior persistence with vedolizumab also at 24 months (76.3 vs 52.4% and 78.5 vs 63.5%, respectively) [8,9], and at 5 years [14]. These findings highlight the complementary role of real-world studies to network meta-analyses in informing drug positioning in ulcerative colitis. Interestingly, none of the available network meta-analyses [16,17] suggested the possibility of superiority of first-line vedolizumab compared to anti-TNF agents. This probably reflects differences in real-world and clinical trial populations, as well as divergent definitions of treatment success. Nonetheless, concordant findings from numerous independent cohort studies cited above, describing outcomes beyond the usual duration of a randomized controlled trial lend support for the use of vedolizumab as the first-line biologic in ulcerative colitis.

Contrary to our findings in ulcerative colitis, no significant differences were observed in treatment persistence for anti-TNF agents, vedolizumab, and ustekinumab in Crohn's disease, although the latter two agents had numerically higher persistence. Data on differences in persistence of first-line biologics in Crohn's disease are heterogeneous [6,14,18], with studies either showing no difference [14,19] or suggesting superiority of either anti-TNF agents [18] or ustekinumab [6]. It should be noted that drug approval timelines and local reimbursement rules have limited the number of studies where all three classes of biologics could be compared by their first-line effectiveness. The PANIC cohort was the first to report on the persistence of anti-TNF agents, vedolizumab, and ustekinumab [6]. Treatment persistence at 1 year with first-line ustekinumab was 93%, 90% with vedolizumab, and 85% with anti-TNF agents. At 3 years of follow-up, persistence with ustekinumab remained high at 83%. The relative effectiveness of first-line biologics remains to be determined in the real-world setting, whereas the only available head-to-head trial did not demonstrate a significant difference between adalimumab and ustekinumab [5].

Treatment persistence in our study was adjusted for patient age, gender, disease duration, disease location (Crohn's disease), disease extent (ulcerative colitis), and treatment period (before and after unrestricted use of all three classes of biologics in 2019), which strengthens the validity of our findings. A notable finding was that disease extent and location did not interact with treatment type to impact treatment persistence, suggesting that these

factors are not of critical importance when selecting a specific drug. Moreover, disease duration did not impact persistence of the first-line biologic – neither in Crohn's disease nor in ulcerative colitis. This is a well-established observation in ulcerative colitis, where the effectiveness of the first-line biologic is preserved regardless of disease duration, which has been shown in an individual-patient meta-analysis [20] and cohort studies [21–24]. In Crohn's disease, evidence points toward higher remission rates with shorter disease duration [20]. To some extent, disease duration may be confounded with prior exposure to biologics: a subset of patients who required treatment with a biologic later in the course of the disease could have a more indolent disease course [25,26], which could perhaps attenuate the impact of disease duration on the effectiveness of the first biologic. An additional potential explanation lies in the outcome definition, with treatment persistence being somewhat less stringent and conceivably less sensitive to detect a decrement in effectiveness with longer disease duration.

While treatment persistence captures the effectiveness, safety, and tolerability of treatment in the real-world setting, it is not a treatment goal in IBD. Conceivably, an ineffective treatment which offers suboptimal disease control could still be continued in the absence of therapeutic alternatives. To address this potential source of bias, we also assessed symptomatic remission at end of follow-up in the subset of patients who were still receiving the first-line biologic at the end of follow-up. No differences in remission rates were observed in Crohn's disease, whereas the proportion of patients with ulcerative colitis in remission was higher with anti-TNF agents, compared to vedolizumab, which contrasts with our results on treatment persistence. Although our study was not designed to explore the cause of the divergence between treatment persistence and disease control, a potential explanation is that patients and clinicians were willing to tolerate slightly inferior disease control in exchange for the perceived superior safety profile of vedolizumab. Data on the relative safety of vedolizumab compared with anti-TNF agents are equivocal, yet cohort studies lend some support to the notion of vedolizumab being safer [9], which may have affected management decisions.

An advantage of our study is the adjustment of treatment persistence for relevant disease-related covariates. A further strength is the absence of restrictions for prescribing first-line biologics since 2019, which enabled comparison of the three main therapeutic classes. Limitations include the absence of data on disease activity upon prescription of the biologic, data on combination treatment with immunosuppressants, dose escalations of biologicals, and the use of corticosteroids. Additional covariates not adjusted for, may also have impacted treatment persistence. Nevertheless, we aimed to provide causal interpretation even though observational data was used. Simply reporting Kaplan–Meier survival estimates and hazard ratios would not allow any adjustments for confounders as hazard ratios cannot deal with changes over time and have inherent selection bias [11]. The applied approach (Hernan 2010) provided survival curves adjusted for baseline confounders. This simple and straightforward approach is one of many to address this issue (e.g. propensity score analysis, inverse probability of treatment weighting, g-formula) [11]. Only a sufficiently powered randomized trial over 3–4 years could directly compare effectiveness of the three classes of biologicals. Unfortunately, it is very unlikely that such a trial will be conducted in the near future for drugs with expired patent. Consequently, real-life data remain the main source for informing patients and physicians on the expected benefit of biologicals prescribed in first line. Future registration trials are likely to address this at an early stage of drug development as evidenced in a recent trial of p19 inhibitor risankizumab [27].

In this registry-based single center cohort study we found that anti-TNF agents, vedolizumab, and ustekinumab had comparable treatment persistence as first-line biologics in Crohn's disease. In ulcerative colitis, first-line vedolizumab had longer treatment persistence anti-TNF agents, although the rates of symptomatic remission in patients still on treatment with the first-line biologic at the end of follow-up were slightly lower for vedolizumab than anti-TNF agents.

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E.S. contributed in the conceptualization, data curation, investigation, methodology, software, validation, data visualization, writing – original draft preparation, and writing – review and editing. J.H. contributed in the conceptualization, data curation, investigation, methodology, supervision, validation, writing – original draft preparation, and writing – review and editing. G.N. contributed in the data curation, investigation, writing – original draft preparation, and writing – review and editing. D.M. contributed in the data curation, formal analysis, methodology, data visualization, writing – original draft preparation, and writing – review and editing. B.Š. contributed in the conceptualization, project administration, supervision, validation, and writing – review and editing. D.D. contributed in the conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, writing – original draft preparation, and writing – review and editing. All authors have read and agreed to the published version of the manuscript.

This study was approved by the National Medical Ethics Committee of Slovenia (ID 0120-576/2019/7). All patients signed informed consent.

The patients gave consent for publication as part of consent to participate in the study.

Data available on request from the authors.

Conflicts of interest

J.H. has served as a consultant for Abbvie, Alimentiv Inc., Janssen, and Takeda. G.N. has served as a speaker, consultant, and advisory board member for Abbvie, Takeda, Pfizer, Janssen, Oktal Pharma, Sobi, Krka, Sandoz, and Biogen. B.Š. served as a speaker, a consultant, and/or an advisory board member for MSD, Abbvie, Takeda, Pfizer,

and Janssen. D.D. has served as a speaker, consultant, and/or advisory board member for MSD, Abbvie, Takeda, Pfizer, Janssen, Krka, Eli Lilly, Oktal Pharma, Roche, Novartis, Amgen, and Lek. For the remaining authors, there are no conflicts of interest.

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