Utilisation of biologicals in inflammatory bowel disease in Slovenia – report from UR-CARE registry for the year 2022

Uporaba bioloških zdravil pri bolnikih s kronično vnetno črevesno boleznijo v Sloveniji – podatki iz UR-CARE registra za leto 2022

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***Ključne besede**: epidemiologija, vzorci zdravljenja, vztrajanje z zdravljenjem*

ABSTRACT

Background. Due to the increasing incidence of inflammatory bowel disease (IBD) many patients are being treated with biological drugs. However, real-world treatment patterns with biologicals in Slovenian IBD patients have not yet been reported.

Aim. To characterise biological drug use in Slovenian IBD centres until the year 2022.

IZVLEČEK

Izhodišča. Zaradi naraščajoče incidence kronične vnetne črevesne bolezni (KVČB) je vse več bolnikov zdravljenih z biološkimi zdravili. Kljub temu v Sloveniji nimamo podatkov o vzorcih zdravljenja z biološkimi zdravili pri naših bolnikih.

Namen. Opredeliti uporabo bioloških zdravil v slovenskih centrih za KVČB v letu 2022.

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Material and Methods. We analysed data on the biological treatment of IBD patients from the UR-CARE Registry (initiated in October 2020) with data lock on 1st October 2022.

Results. Out of 2748 IBD patients treated in Slovenian IBD centres in the year 2022, 1014 of Crohn's disease (CD) and 623 of ulcerative colitis (UC) patients received biological therapy. TNF-alpha inhibitors were preferred as first-line therapy: adalimumab for CD (39.5%) and infliximab for UC (38.8%). Ustekinumab dominated second and third-line biological therapy in CD (28.9%, 43.1%, respectively) and vedolizumab in UC (36.8%, 43.3%, respectively). Over half of patients persisted with their first-line treatment (CD 58.2%, UC 57.8%) at the end of follow-up. Persistence rates were higher for first-line vedolizumab (CD 75.8%, UC 75.1%) and ustekinumab (CD 75.2%, UC 94.4%) than for TNF-alpha inhibitors (infliximab: CD 55.8%, UC 49.6%, adalimumab: CD 49.9%, UC 37.3%).

Conclusions. Biological treatment patterns in Slovenia were comparable with those in the European Union. TNF-alfa inhibitors remain the most common choice for first biological.

Metode. Analizirali smo podatke o biološkem zdravljenju bolnikov s KVČB, zbrane v UR-CARE registru v obdobju od formacije registra oktobra 2020 do 1. oktobra 2022.

Rezultati. Do leta 2022 je bilo v slovenski UR-CARE register vnesenih 2748 bolnikov iz 6 slovenskih KVČB centrov. Od tega je biološko terapijo prejelo 1014 bolnikov s Crohnovo boleznijo (CB) in 623 bolnikov z ulceroznim kolitisom (UK). Kot zdravilo prvega reda so bili najpogosteje predpisani zaviralci TNF-alfa: adalimumab pri CB (39,5 %) in infliximab pri UK (38,8 %). Kot zdravilo drugega in tretjega reda pa ustekinumab pri CB (28,9 % in 43,1 %) in vedolizumab pri UK (36,8 % in 43,3 %). Ob izvozu podatkov iz registra je več kot polovica vseh bolnikov vztrajala z zdravilom prvega reda (CB 58,2 %, UK 57,8 %), pri čemer je bil delež vztrajajočih višji na vedolizumabu (CB 75,8 %, UK 75,1 %) in ustekinumabu (CB 75,2 %, UK 94,4 %) kot na zaviralcih TNF-alfa (infliximab: CB 55,8 %, UK 49,6 %, adalimumab: CB 49,9 %, UK 37,3 %).

Zaključki. Vzorci predpisovanja bioloških zdravil v Sloveniji so podobni kot v drugih državah v Evropski uniji. Zaviralci TNF-alfa ostajajo najbolj pogosto predpisana biološka zdravila prvega reda do leta 2022.

INTRODUCTION

The incidence of inflammatory bowel disease (IBD) is increasing worldwide. It is estimated that currently 1 in 300 Europeans are affected (1). The disease is immune-mediated and may have a difficult course; therefore, many patients need treatment with biological drugs to prevent serious complications and intestinal failure. However, data on biological treatment in Slovenian IBD patients is lacking since these data have not been collected systematically until recently. In 2019 Slovenia started UR-CARE Registry. Until the year 2022, six Slovenian IBD centres joined the UR-CARE Registry. These six centres systematically enter data on patient characteristics and drug use into the registry. Consequently, data on biological drug use is now available in Slovenia.

This report aimed to analyse biological drug use until the year 2022 in Slovenia across all IBD centres included in the registry.

MATERIALS AND METHODS

In this study, we analysed the biological treatment of inflammatory bowel disease (IBD) patients in Slovenia in the year 2022. Patient data was prospectively collected from the UR-CARE Registry with data lock on 1st October 2022. The registry included data from the following medical centres: University Medical Centre Ljubljana (UMC Ljubljana), University Medi-

cal Centre Maribor (UMC Maribor), General Hospital Celje (GH Celje), General Hospital Jesenice (GH Jesenice), General hospital Izola (GH Izola) and Diagnostic centre Bled (DC Bled).

After the export of the data from the UR-CARE registry data collection and analyses were performed using Microsoft Excel software (version 2301, build 16.0.16026.20196). Descriptive statistics are presented as the means ± standard deviations for parametric variables and percentages for categorical variables. This study was approved by the National Medical Ethics Committee of Slovenia (ID 0120-576/2019/7).

RESULTS

Patient characteristics

At this data lock the UR-CARE Registry included 2748 patients with IBD. Most patients were diagnosed with Crohn's disease (51.1%), followed by ulcerative colitis (45.0%) and only a few who were diagnosed with IBD unclassified (3.5%). The genders were equally distributed. The median patient's age at diagnosis was 36.6 years (standard deviation (SD) 16.1). The majority of patients (42.6%) have never smoked. A minority of patients (6.4%) had a family history of inflammatory bowel disease. Patient demographics are shown in Table 1.

Disease phenotype

In most medical centres the majority of patients were diagnosed with Crohn's disease, except in GH Jesenice and in DC Bled, where more patients were diagnosed with ulcerative colitis. The proportion of Crohn's disease patients with risk factors for complications (i.e. ileal disease and perianal disease) was similar between all centres with exceptions again being GH Jesenice and DC Bled (more patients had ileal disease and fewer had perianal disease). In total, perianal disease was detected in 264 (18.8%) out of 1405 patients with Crohn's disease. Patients with Crohn's disease were generally a few years younger at the time of diagnosis than patients with ulcerative colitis and were diagnosed earlier in university clinical centres than in general hospitals or diagnostic centres. Overall characteristics of patients were similar between all medical centres. Phenotype data for every IBD centre are shown in Table 2.

Biological drug use in patients with Crohn's disease and ulcerative colitis

In total, 1014 patients with Crohn's disease received 1690 treatment episodes with biological drugs. The

Table 1. Patient characteristics

	All patients (n = 2748)
Current age [years]	47.3 ± 14.8
Age at diagnosis [years]	36.6 ± 16.1
Gender	
Male	1367 (49.7%)
Female	1358 (49.4%)
Missing information	23 (0.8%)
Diagnosis	
Crohn's disease	1405 (51.1%)
Ulcerative colitis	1237 (45.0%)
Unclassified inflammatory bowel disease	95 (3.5%)
Missing data	11 (0.4%)
Smoking	
Yes	293 (10.7%)
Previous smoker	406 (14.8%)
No	1170 (42.6%)
Info not available	458 (16.7%)
Missing info	421 (15.3%)
Family history of inflammatory bowel disease	
Yes	176 (6.4%)
No	1752 (63.8%)
Info not available	375 (13.6%)
Missing info	445 (16.2%)

Table 2. Disease phenotype in 6 inflammatory bowel disease centres in Slovenia

	University Medical Centre Ljubljana	University Medical Centre Maribor	General hospital Celje	General hospital Izola	General hospital Jesenice	Diagnostic centre Bled
Total number of patients with IBD***	1950	369	183	194	29	23
CD* - N (%)	967 (49.6%)	224 (61.5%)	95 (51.9%)	104 (53.6%)	10 (34.5%)	5 (21.7%)
UC** - N (%)	910 (46.7%)	130 (35.7%)	83 (45.4%)	81 (41.8%)	17 (58.6%)	16 (69.6%)
IBD-U*** - N (%)	73 (3.7%)	10 (2.7%)	4 (2.2%)	6 (3.1%)	1 (3.4%)	1 (4.3%)
Crohn's with isolated ileum disease - N (% of all CD)	248 (25.6%)	38 (17.0%)	17 (17.9%)	17 (16.3%)	4 (40.0%)	2 (40.0%)
Crohn's with ileocolonic disease - N (% of all CD)	62 (6.4%)	7 (3.1%)	7 (7.4%)	7 (6.7%)	1 (10.0%)	0
Crohn's perianal - N (% of all CD)	176 (18.2%)	53 (23.7%)	20 (21.0%)	14 (13.5%)	1 (10.0%)	0
Age at diagnosis CD	30.6±18.0	34.0±17.1	36.3±17.6	38.5±18.0	37.8±9.0	38.5±17.7
Age at diagnosis UC	35.4±17.4	39.4±17.1	36.3±14.2	39.4±17.2	31.6±15.2	41.8±16.9
Extraintestinal manifestitations - N (% of all IBD patients)	241 (12.4%)	38 (10.3%)	32 (17.5%)	19 (9.8%)	4 (13.8%)	4 (17.4%)

*****IBD-U – IBD – indeterminate*
**CD – Crohn's disease; **UC – ulcerative colitis; ***IBD – inflammatory bowel disease*

most commonly prescribed first-line treatments were TNF-alpha inhibitors adalimumab (39.5%) and infliximab (36.6%). As a second, third and fourth line of treatment, the most frequently prescribed biologic was ustekinumab (28.9%, 43.1%, 45.9%, respectively), followed by vedolizumab (17.1%, 23.4%, 23.0%, respectively). Detailed prescription sequence of biologics in CD is shown in Table 3.

In UC, 623 patients received 1010 treatment episodes with biologics in total. As a first-line treatment infliximab (38.8%) was the most common drug of choice. As a second and third-line drug vedolizumab was the most frequently prescribed among all biologic (36.8%, and 43.3%, respectively) and ustekinumab as a fourth and fifth line of treatment (50.0%, 66.7%, respectively). The detailed prescription sequence of biologics in UC is shown in Table 4.

Ongoing biological treatment in Crohn's disease and ulcerative colitis

Out of 1014 patients with CD 590 (58.2%) were still treated with a first-line biologic at the time of data export, 223 (22.0%) with a second line and 82 (8.1%) with a third-line biologic. The proportion of patients that persisted with the first-line biologic was the highest for vedolizumab (100/132, 75.8%), followed by ustekinumab (82/109, 75.2%), infliximab (207/371, 55.8%) and adalimumab (200/401, 49.9%). Several patients with CD that persisted on specific biological are shown in Table 5.

Out of 623 patients with UC 360 (57.8%) were still being treated with a first-line biologic, 106 (17.0%) with a second line and 50 (8.0%) with a third-line biologic. The proportion of patients that persisted with the first-line biologic was the highest for ustekinumab

Table 3. Number of prescriptions (treatment episodes) in respective lines of therapy for Crohn's disease

Line	All	Adalimumab/ biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab/ biosimilars	Infliximab/ Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	1014	135 (13.3%)	266 (26.2%)	0 (0%)	0 (0%)	207 (20.4%)	164 (16.2%)	1 (0.1%)	0 (0%)	109 (10.7%)	132 (13.0%)
Second line	432	25 (5.79%)	97 (22.5%)	0 (0%)	0 (0%)	71 (16.4%)	40 (9.3%)	0 (0%)	0 (0%)	125 (28.9%)	74 (17.1%)
Third line	167	5 (3.0%)	20 (12.0%)	0 (0%)	0 (0%)	22 (13.2%)	8 (4.8%)	0 (0%)	1 (0.6%)	72 (43.1%)	39 (23.4%)
Fourth line	61	4 (6.6%)	5 (8.2%)	0 (0%)	1 (1.6%)	6 (9.8%)	3 (4.9%)	0 (0%)	0 (0%)	28 (45.9%)	14 (23.0%)
Fifth line	15	1 (6.7%)	2 (13.3%)	2 (13.3%)	0 (0%)	2 (13.3%)	0 (0%)	0 (0%)	0 (0%)	5 (33.3%)	3 (20.0%)
Sixth line	1	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	1690	171 (10.1%)	390 (23.1%)	2 (0.1%)	1 (0.06%)	308 (18.2%)	215 (12.7%)	1 (0.06%)	1 (0.06%)	339 (20.1%)	262 (15.5%)

Table 4. Number of prescriptions (treatment episodes) in respective lines of therapy for ulcerative colitis

Line	All	Adalimumab biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab biosimilars	Infliximab Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	623	17 (2.7%)	50 (8.0%)	61 (9.8%)	0 (0%)	152 (24.4%)	90 (14.4%)	0 (0%)	0 (0%)	36 (5.8%)	217 (34.8%)
Second line	253	8 (3.2%)	40 (15.8%)	11 (4.3%)	0 (0%)	55 (21.7%)	22 (8.7%)	0 (0%)	0 (0%)	24 (9.5%)	93 (36.8%)
Third line	104	3 (2.9%)	7 (6.7%)	4 (3.8%)	0 (0%)	15 (14.4%)	3 (2.9%)	0 (0%)	1 (1.0%)	26 (25.0%)	45 (43.3%)
Fourth line	24	1 (4.2%)	0 (0%)	1 (4.2%)	0 (0%)	2 (8.3%)	4 (16.7%)	0 (0%)	0 (0%)	12 (50.0%)	4 (16.7%)
Fifth line	6	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (66.7%)	1 (16.7%)
Sixth line	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	1010	29 (2.9%)	98 (9.7%)	77 (7.6%)	0 (0%)	224 (22.2%)	119 (11.8%)	0 (0%)	1 (0.1%)	102 (10.1%)	360 (35.6%)

Table 5. Number of patients, who remained on biologic in respective line of treatment for Crohn's disease

Line	All	Adalimumab biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab biosimilars	Infliximab Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	590	89 (15.1%)	111 (18.8%)	0 (0%)	0 (0%)	143 (24.2%)	64 (10.8%)	1 (0.2%)	0 (0%)	82 (13.9%)	100 (16.9%)
Second line	223	12 (5.4%)	23 (10.3%)	0 (0%)	0 (0%)	43 (19.3%)	6 (2.7%)	0 (0%)	0 (0%)	106 (47.5%)	33 (14.8%)
Third line	82	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	11 (13.4%)	1 (1.2%)	0 (0%)	0 (0%)	50 (61.0%)	19 (23.2%)
Fourth line	36	1 (2.8%)	4 (11.1%)	0 (0%)	1 (2.8%)	2 (5.6%)	1 (2.8%)	0 (0%)	0 (0%)	22 (61.1%)	5 (13.9%)
Fifth line	10	1 (10.0%)	0 (0%)	1 (10.0%)	0 (0%)	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)	5 (50.0%)	2 (20.0%)
Sixth line	1	1 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	942	105 (11.1%)	138 (14.6%)	1 (0.1%)	1 (0.1%)	200 (21.2%)	72 (7.6%)	1 (0.1%)	0 (0%)	265 (28.1%)	159 (16.9%)

(34/36, 94.4%), followed by vedolizumab (163/217, 75.1%), infliximab (120/242, 49.6%), adalimumab (25/67, 37.3%) and golimumab (18/61, 29.5%). Number of patients with UC that persisted with biological treatment is shown in Table 6.

Table 6. Number of patients, who remained on biologic in respective line of treatment for ulcerative colitis

Line	All	Adalimumab biosimilars	Adalimumab/ Humira	Golimumab	Guselkumab	Infliximab biosimilars	Infliximab Ramicade	Natalizumab	Risankizumab	Ustekinumab	Vedolizumab
First line	360	9 (2.5%)	16 (4.4%)	18 (5.0%)	0 (0%)	89 (24.7%)	31 (8.6%)	0 (0%)	0 (0%)	34 (9.4%)	163 (45.3%)
Second line	106	5 (4.9%)	8 (7.5%)	2 (1.9%)	0 (0%)	24 (22.6%)	2 (1.9%)	0 (0%)	0 (0%)	17 (16.0%)	48 (45.3%)
Third line	50	0 (0%)	1 (2.0%)	1 (2.0%)	0 (0%)	6 (12.0%)	0 (0%)	0 (0%)	0 (0%)	20 (40.0%)	22 (44.0%)
Fourth line	11	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	1 (9.1%)	0 (0%)	0 (0%)	8 (72.7%)	1 (9.1%)
Fifth line	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (100.0%)	0 (0%)
Sixth line	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total*	531	14 (2.6%)	25 (4.7%)	21 (4.0%)	0 (0%)	120 (22.6%)	34 (6.4%)	0 (0%)	0 (0%)	83 (15.6%)	234 (44.1%)

DISCUSSION

In this study, we report on biological drug utilization in Slovenia until the year 2022. Our most important finding is that biological drug use in Slovenia follows that of Western Europe suggesting that Slovenia has good access to advanced treatments. More than half of patients were still approached with TNF-alpha inhibitors as a first-line treatment. However, an important proportion of patients received second-generation biological vedolizumab and ustekinumab as first-line treatment.

The strength of this study is that we reported data on drug use across 6 Slovenian IBD centres, 2 academic and 4 non-academic centres. Here we could observe that the disease phenotype of IBD patients was similar in all Slovenian IBD centres suggesting that IBD teams of respective centres were confident with treating different IBD phenotypes. This can be explained with good access to academic teams which regularly review applications for initiation of biologicals and also advice on tackling the loss of response to these drugs and offer support for severe disease complications.

In general, the disease phenotype of IBD and disease location of Slovenian patients were comparable with those reported by others (2). The same was observed for extraintestinal manifestations (3). Approximately one-quarter of CD patients had a perianal fistulizing disease which is in line with other cohorts (18.8%) (4–7).

Biological treatment patterns were in line with other studies (8). Namely, most patients received TNF-alpha inhibitors as a first-line treatment. In CD, adalimumab and infliximab were prescribed with equal frequencies. However, in UC infliximab was prescribed almost four times more frequently than adalimumab or golimumab, presumably due to its superior durability (9–11). As reported by others, ustekinumab was more commonly used than vedolizumab in Crohn's disease and the reverse was true for ulcerative colitis (9, 12, 13). Here it should be stressed that we only reported total drug use until 2022. Unfortunately, we were unable to analyse changing trends of drug choice over time in this early report. This might be relevant as drug prescription changed dramatically after the year 2019 when constraints on choice of first-line biological were released in Slovenia.

In both, Crohn's disease and ulcerative colitis, around 58% of patients were still being treated with their first-line biological at the time of data export. In other studies, persistence rates declined with every line of treatment (14, 15). The proportion of CD and UC patients that persisted with their first-line biologic was higher for vedolizumab and ustekinumab in comparison with TNF-alpha inhibitors. This is in line with the recent VARSITY trial (16) and several real-life cohorts (12, 14).

Our study has several limitations. The most important limitation of this early report is that data entry might not be complete in all IBD centres in Slovenia, particularly in those which only recently joined the URCARE registry. We also did not include data on Janus kinase inhibitors as in the year 2022 only a few patients (compared to biologicals) were treated with these molecules. Also, most IBD centres did not report on dose optimisation of biologicals although these data would be important for a more accurate understanding of biological drug utilisation in Slovenia. In addition, we failed to include data on conventional treatments, thus we were unable to assess the proportion of patients treated with biologicals in Slovenia.

In summary, the utilisation of biologicals in IBD in Slovenia is similar to that in other countries of the European Union. Inhibitors of TNF-alfa were the most common choice for first-line biological in Slovenia until 2022. After the failure of TNF-inhibitor(s), ustekinumab was the most prescribed drug for Crohn's disease and vedolizumab in ulcerative colitis until the year 2022.

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