Clinical Rheumatology (2019) 38:297–305
https://doi.org/10.1007/s10067-018-4324-7

ORIGINAL ARTICLE

The persistence of golimumab compared to other tumour necrosis factor-α inhibitors in daily clinical practice for the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: observations from the Slovenian nation-wide longitudinal registry of patients treated with biologic disease-modifying antirheumatic drugs—BioRx.si

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Received: 25 June 2018 / Revised: 27 September 2018 / Accepted: 4 October 2018 / Published online: 15 October 2018

Abstract

To assess the persistence of golimumab and other tumour necrosis factor-α inhibitors (TNFis) in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) in Slovenia. We analysed prospectively the collected data of all patients treated with golimumab and other TNFis from 1 January 2010 to 31 July 2018 from the mandatory national BioRx.si registry. We assessed the treatment persistence stratified by treatment type, indication and prior exposure to bDMARDs using the Kaplan-Meier method and Cox proportional regression hazards' models adjusted for the well-appreciated confounders. We also assessed its effectiveness at 1 year after the initiation of therapy. During the 7-year observation period, 24 Slovenian rheumatologists from eight centres contributed data on 368, and 1654 patients treated for 849, and 3321 person-years with golimumab and other TNFis, respectively. The overall proportions of RA, AS and PsA patients being persistent on golimumab vs. other TNFis at 2 years after starting the therapy did not differ significantly and were 53%, 67% and 59% vs. 47%, 65% and 59%, respectively. The crude and adjusted hazard ratios for golimumab discontinuation did not differ significantly between bDMARD-naïve and bDMARD-experienced patients for any of the indications. In contrast, bDMARD-experienced AS and PsA patients treated with other TNFis were significantly more likely to discontinue treatment. The persistence of golimumab in patients with RA, AS and PsA in Slovenia was comparable with its persistence in more affluent Western European countries. We observed a better persistence of golimumab compared to other TNFis in bDMARD-experienced AS and PsA patients.

Keywords Ankylosing spondylitis · Biologic agents · Psoriatic arthritis · Rheumatoid arthritis

Introduction

Golimumab is one of the several tumour necrosis factor-α inhibitors (TNFis) indicated to treat rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). It has a comparable efficacy and safety to other TNFi with the advantage of the longest dosing interval among the subcutaneously administered TNFis [1–5].

The retention rates, surrogate markers of efficacy and tolerability, after completing 5 years of follow-up in the open label extensions of the landmark trials, were about 60% of patients with RA, 72% with AS and 69% with PsA [6]. The internal validity of the clinical trials of TNFi is robust. However, due to the strict inclusion and exclusion criteria, less than 10% of the population treated in daily clinical practice would be eligible to enter these trials [7]. Longitudinal observational studies have been set up to test the external validity of the results of the clinical trials. By nature of their design, these studies are subject to irregular follow-up time points,

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incomplete data and biases, often making the data analysis, and the interpretation of the results, challenging. In this setting, it is convenient to assess the treatment persistence, a surrogate marker of both effectiveness and tolerability.

The persistence of golimumab in RA, AS and PsA in the real-world setting was lower than the retention in the open label extensions of the landmark trials [8–12]. Some of these real-world studies lumped the patients with these three different diseases together [11], and some only considered RA patients [10, 12], and some only bDMARD-naïve patients [10, 11], while only one included a comparator group of patients treated with other TNFis or other bDMARDs [12]. Notably, most of these observations came from the registries in high-income countries and may not be transferable to lower-income Central European countries like Slovenia due to differences in targeted DMARD accessibility, prescription restrictions and reimbursement [13].

The aims of the presented study were primarily to assess the persistence of golimumab, and secondarily to compare it to the persistence of other TNFis in patients with RA, AS and PsA in the Central European, European Union member state Slovenia.

Patients and methods

Patients and setting

We analysed prospectively the collected data of all patients treated with golimumab and other TNFis (i.e. adalimumab, etanercept, certolizumab and infliximab) as comparators from 1 January 2010 to 31 July 2018 from the BioRx.si registry which was previously described in detail [14]. In short, the mandatory national registry, established in February 2008, contains demographic, effectiveness and safety data of patients with RA, AS and PsA treated with bDMARDs. The patients are classified in accordance with the modified 1987 ACR criteria, or EULAR/ACR 2010 criteria for RA, the modified 1984 New York criteria for AS and the CASPAR criteria for PsA [15–18].

In Slovenia, bDMARDs are usually used after patients with RA or PsA fail two csDMARDs, and patients with AS fail at least two non-steroidal anti-inflammatory drugs. They are chosen jointly by the patient and their attending rheumatologist and are fully reimbursed by the national health insurance. The attending rheumatologists are the sole prescribers of bDMARDs in these patients. The disease activity, safety and treatment data are collected by all Slovenian rheumatologists every 3 months during the first year of treatment, and every 6 months thereafter if the patient is stable on the current therapy.

Outcome measures

The primary outcome was the persistence of the golimumab by indication and prior bDMARD exposure. The secondary outcome was the treatment effectiveness after 1 year of therapy. To assess effectiveness, we used a disease activity score based on a 28-joint count and erythrocyte sedimentation rate (DAS28ESR) for RA and PsA patients and ASDAS-CRP for AS patients. For comparison, we also assessed these outcome measures in patients treated with other TNFis during the same observation period.

Statistical analysis

We used standard descriptive statistical methods to summarise the baseline characteristics of our study population after performing multiple imputations with chained equations for missing baseline data. For continuous variables, we used the two-sample Student's *t* test if they were normally distributed, the Mann-Whitney test for the rest and the Chi-square test for categorical variables to assess the differences between the groups. Kaplan-Meier curves were constructed to assess the crude persistence of golimumab and other TNFi therapies for the three diseases, stratified by the prior bDMARD exposure status using the log rank test to test for differences between the strata. Additionally, we calculated the crude and adjusted hazard ratios using the Cox-proportional regression hazard models. Patients who did not stop their therapy by the time of the last recorded observation were lost to follow-up, interrupted therapy due to pregnancy, remission or on the patients' demand were censored. In all univariate Cox analyses stratified by indication, we considered treatment type (i.e. golimumab or other TNFi), patient age, gender, year of treatment initiation, and past bDMARD exposure, baseline PromisHAQ, pain and smoking status. In the RA group, we additionally considered the rheumatoid factor and ACPA positivity, past and concomitant csDMARD, glucocorticoid exposure and baseline DAS28ESR. In the AS group, we additionally considered HLA-B27 status, baseline BASDAI, ASDAS-CRP, and in the PsA group HLA-B27 positivity, and baseline DAS28ESR.

We assessed the treatment's effectiveness after 1 year according to the last observation carried forward imputation for missing data.

We analysed the data using R 3.5.1, Vienna, Austria with tidyverse, mice and survminer packages.

Results

The study population

During the more than 7-year observation period, the 24 Slovenian rheumatologists from two tertiary and six secondary centres contributed data on 368 and 1654 patients who started the treatment of RA, AS or PsA with either golimumab or other TNFi, respectively. The total exposure to golimumab

and other TNFis were 849 and 3321 person-years, respectively. In Table 1, we present the characteristics of the patients at the initiation of golimumab or other TNFi treatment.

Overall persistence of golimumab vs other TNFis

The overall proportions of RA, AS and PsA patients persisting on golimumab treatment 1 year after starting the treatment were 66% (95% CI 58–75%), 78% (95% CI 71–85%) and 72% (95% CI 63–83%), and 2 years after starting the therapy were 53% (95% CI 44–64%), 67% (95% CI 60–76%) and 59% (95% CI 49–72%), respectively. The overall proportions of RA, AS and PsA patients persisting on other TNFis 1 year after starting the treatment were 60% (95% CI 57–64%), 75% (95% CI 71–79%) and 70% (95% CI 64–75%), and 2 years after starting the therapy were 47% (95% CI 43–50%), 65% (95% CI 60–70%) and 59% (95% CI 53–65%), respectively (Fig. 1, top two panels). The crude persistence rates differed significantly by indication in the other TNFi treatment group. This difference was lost after adjusting for the patient's age.

The hazards' ratios for treatment discontinuation using both crude and adjusted (shown here) Cox-models were comparable between golimumab (HR 1.0) and other TNFis in RA (HR 1.2, 95% CI 0.9–1.5, $p = 0.258$), AS (HR 1.1, 95% CI 0.8–1.5, $p = 0.578$) and PsA (HR 1.0, 95% CI 0.7–1.4, $p = 0.856$).

Overall, in the RA group, a higher DAS28ESR and treatment with glucocorticoids at baseline were the only predictors significantly influencing the persistence in the univariate Cox-models. This was confirmed in the multivariate Cox-model that included treatment type, year of treatment initiation, patient age, gender, rheumatoid factor, baseline DAS28ESR, concomitant treatment with glucocorticoids and csDMARDs. A higher DAS28ESR (HR 1.1, 95% CI 1.0–1.2, $p = 0.012$) and glucocorticoids at baseline (HR 1.5, 95% CI 1.2–1.7, $p < 0.0001$) were associated with worse persistence.

In the AS group, the univariate analysis showed a better persistence in bDMARD-naïve (HR 0.59, 95% CI 0.46–0.77, $p < 0.0001$) and HLA-B27-positive (HR 0.73; 95% CI 0.53–0.99, $p = 0.046$) patients, and a worse persistence among the females (HR 1.50, 95% CI 1.10–1.90, $p = 0.003$), the patients with a higher baseline BASDAI (HR 1.10, 95% CI 1.00–1.20, $p = 0.022$) and the past or current smokers (HR 1.30, 95% CI 1.00–1.70, $p = 0.033$). The results of the multivariate Cox model, which included treatment type and variables found to be significant in the univariate analysis, did not differ from the results of the univariate analyses.

In the PsA group, the univariate analysis showed a better persistence in bDMARD-naïve (HR 0.65, 95% CI 0.49–0.88, $p = 0.005$) and a worse persistence among the females (HR 1.50, 95% CI 1.10–2.00, $p = 0.009$) and those with higher baseline DAS28ESR (HR 1.10, 95% CI 1.00–1.20, $p = 0.04$). In the multivariate analysis, which included the treatment type, the year of treatment initiation and the confounders that were identified as possibly significant in the univariate analysis, only the bDMARD-naïve status (HR 0.66, 95% CI 0.48–0.89, $p = 0.006$) remained significantly associated with a better treatment persistence.

The persistence of golimumab vs. other TNFi by indication and past bDMARD exposure

The crude and adjusted persistence rates in bDMARD-naïve and bDMARD-exposed RA patients in both golimumab and other TNFi groups were comparable. The crude and adjusted persistence rates in bDMARD-naïve and bDMARD-exposed AS and PsA patients were comparable in the golimumab group and significantly lower for bDMARD-exposed patients in the other TNFi group, respectively (Fig. 1, bottom three panels; Table 2).

The effectiveness of golimumab vs. other TNFis 1 year after the initiation of therapy

Among RA patients treated with golimumab vs. other TNFis, the mean (standard deviation, SD) DAS28ESR was 3.60 (1.70) vs. 4.00 (1.54) ($p = 0.01$), with a mean (SD) reduction of − 1.88 (1.68) vs. − 1.86 (1.59), 33% vs. 18% were in DAS28ESR remission and 50% vs. 34% ($p = 0.0002$) in DAS28ESR low disease state, while mean (SD) PromisHAQ was 25 (26) vs. 30 (24) with a mean (SD) reduction of − 14 (23) vs. − 13 (22) ($p = 0.042$), respectively.

Among AS patients treated with golimumab vs. other TNFi, the mean (SD) BASDAI was 3.9 (2.5) vs. 3.7 (2.5), with a mean (SD) reduction of − 3.2 (2.3) vs. − 3.3 (2.5), 47% vs. 51% achieved a 50% reduction of BASDAI from baseline and 65% vs. 70% at least a 2.0 point reduction of BASDAI from baseline. Considering ASDAS-CRP in AS patients treated with golimumab vs. other TNFi, the mean (SD) ASDAS-CRP was 2.15 (1.16) vs. 2.18 (1.18), with a mean (SD) reduction of − 1.70 (1.18) vs. − 1.71 (1.32), respectively. ASDAS improvement/major improvements were achieved by 68%/34% vs. 66%/40% and at least ASDAS low/inactive disease activity state by 54%/22% vs. 54%/25%, respectively. The mean (SD) PromisHAQ was 24 (22) vs. 21 (19) with a mean (SD) reduction of − 12 (20) vs. − 12 (20), respectively.

Among PsA patients treated with golimumab vs. other TNFi, the mean (SD) DAS28ESR was 3.00 (1.41) vs. 3.11 (1.60), with a mean (SD) reduction of − 2.09 (1.48) vs. − 1.86 (1.64), 44% vs. 45% were in DAS28ESR remission and 59% vs. 55% in the DAS28ESR low disease state, while the mean (SD) PromisHAQ was 25 (21) vs. 25 (22) with a mean (SD) reduction of − 15(20) vs. − 11 (22), respectively. None of these outcomes differed significantly.

Table 1 Patient characteristics at the initiation of golimumab or other TNF by indication

Rheumatoid arthritis			
	Golimumab	Other TNFi Adalimumab 35%, Etanercept 30%, Certolizumab 25%, Infliximab 10%	*p*
N	125	874	
% bDMARD-naïve	79	70	0.042
person years	243	1553	
Median past bDMARD count	0 (0–0)	0 (0–1)	0.035
Median follow-up (IQR), years	1.17 (0.46–2.95)	0.96 (0.41–2.66)	0.152
% female	80	83	0.534
% ever smokers	30	31	0.872
Median age (IQR), years	58.9 (50.0–65.5)	56.9 (49.7–64.8)	0.422
Median disease duration (IQR), years	6.4 (2.5–12.4)	5.7 (2.4–11.5)	0.742
% RF+/ACPA+	74/74	75/74	0.809
Median past csDMARD count	3 (2–4)	3 (2–4)	0.116
% csDMARD	76	70	0.187
% glucocorticoids	33	34	0.872
Mean DAS28ESR (SD)	5.54 (1.23)	5.84 (1.26)	0.011
Median CRP (IQR), mg/l	8.4 (1.7–22.0)	10.3 (4.0–25.0)	0.040
Median ESR (IQR), mm/h	28 (14–43)	35 (20–52)	< 0.001
Mean PGA (SD), 0–10	5.8 (2.7)	6.5 (2.4)	0.008
Mean EGA (SD), 0–10	5.0 (2.5)	5.6 (2.2)	0.015
Mean Pain (SD), 0–100	63 (22)	65 (24)	0.544
Mean PromisHAQ (SD), 0–100	39 (23)	43 (24)	0.096
Ankylosing spondylitis			
	Golimumab	Other TNFi Adalimumab 53%, Etanercept 27%, Infliximab 16%, Certolizumab 25%	*p*
N	160	452	
% bDMARD-naïve	64	65	0.843
Total person years	403	1087	
Median past bDMARD count	0 (0–1)	0 (0–1)	0.747
Median follow-up (IQR), years	1.87 (0.59–4.21)	1.46 (0.48–4.21)	0.312
% female	38	40	0.637
Median age (IQR), years	47.3 (39.0–56.1)	46.4 (37.1–55.8)	0.509
Median disease duration (IQR), years	4.7 (1.2–10.1)	5.3 (1.8–13.0)	0.116
% HLAB27+	84	79	0.259
Mean BASDAI (SD)	6.4 (2.0)	6.5 (2.1)	0.400
Mean BASFI (SD)	5.5 (2.5)	5.6 (2.4)	0.582
Mean ASDAS (SD)	3.55 (0.95)	3.64 (1.02)	0.292
Median CRP (IQR), mg/l	8.1 (1.5–20.0)	7.9 (1.6–21.2)	0.566
Median ESR (IQR), mm/h	19 (9–38)	22 (9–40)	0.802
Mean pain (SD), 0–100	68 (20)	68 (22)	0.947
Mean PromisHAQ (SD), 0–100	34 (20)	33 (21)	0.856
Psoriatic arthritis			
	Golimumab	Other TNFi Adalimumab 56%, Etanercept 23%, Infliximab 13%, Certolizumab 8%	P
N	83	328	
% bDMARD-naïve	69	66	0.761
Person years	203	681	
Median past bDMARD count	0 (0–1)	0 (0–1)	0.765
Median follow-up (IQR), years	1.82 (0.67–3.43)	1.35 (0.49–3.28)	0.146
% female	51	48	0.747
Median age (IQR), years	51.0 (44.4–56.6)	50.5 (42.2–57.7)	0.866
Median disease duration (IQR), years	8.8 (4.0–15.5)	5.8 (2.2–12.8)	0.021
% HLAB27+	35	21	0.041
% csDMARD	64	63	1.000
Mean DAS28ESR (SD)	4.93 (1.65)	4.93 (1.47)	0.992
Median CRP (IQR), mg/l	6.0 (2.1–18.0)	6.0 (1.7–16.0)	0.771
Median ESR (IQR), mm/h	25 (7–42)	22 (10–38)	0.944
Mean PGA (SD), 0–10	6.3 (2.9)	6.2 (2.7)	0.733
Mean EGA (SD), 0–10	5.3 (2.6)	5.0 (2.4)	0.439
Mean pain (SD), 0–100	68.35 (22.32)	64.85 (23.36)	0.218
Mean PromisHAQ (SD), 0–100	37.58 (20.96)	35.9 (23.56)	0.528

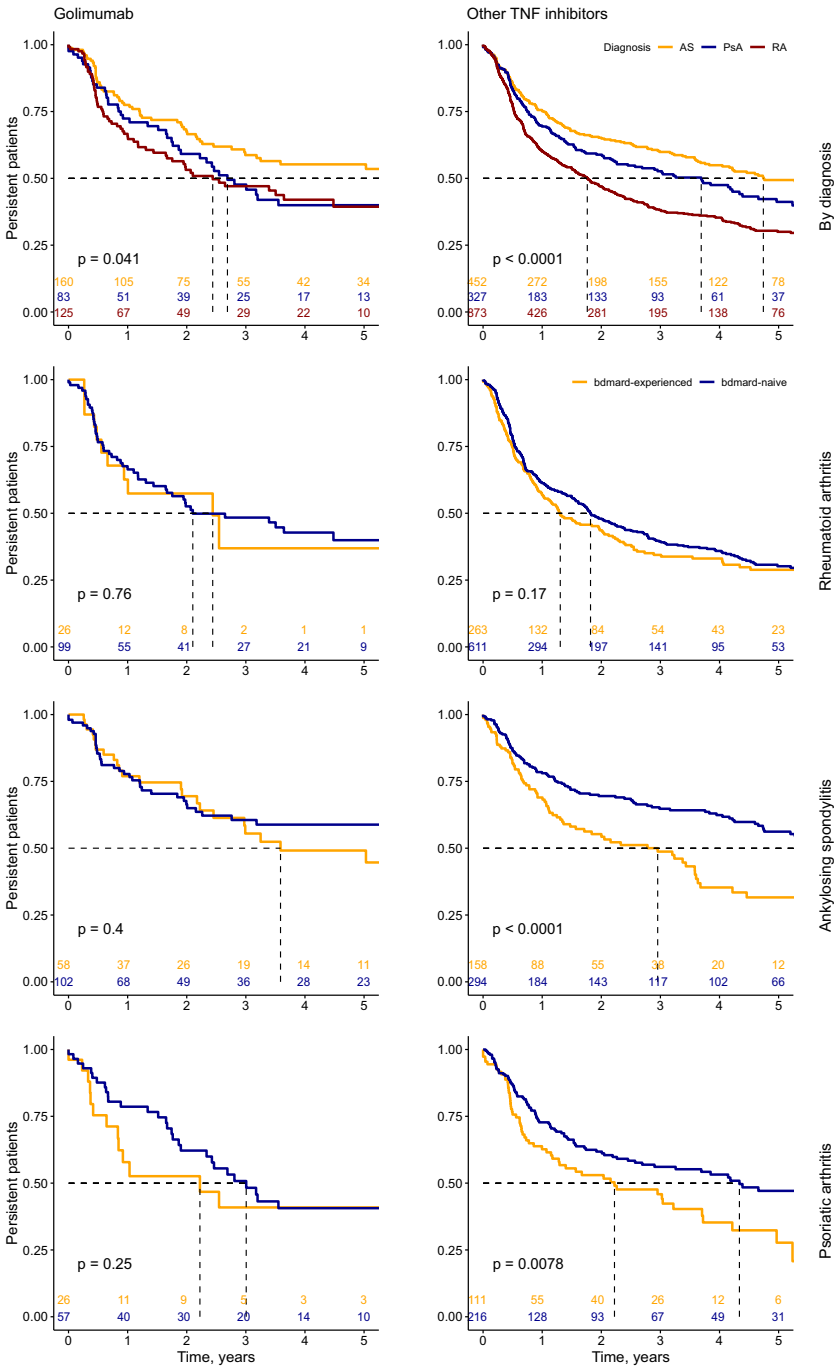

Fig. 1 Persistence of treatment with golimumab by indication and by indication and prior exposure to bDMARDs

Discussion

The analysis of the prospectively collected data from the mandatory Slovenian national on-line registry of patients treated with bDMARDs (BioRx.si) is one of the few real-world studies exploring and comparing the persistence and effectiveness of golimumab to other TNFis, and one of the studies with the longest observation period of 7 years showed that the persistence of golimumab was comparable to the persistence of other TNFis and observations from other real-world reports. Furthermore, the Slovenian data set suggests that prior bDMARD exposure did not significantly influence the persistence of golimumab for any of the studied rheumatic indications, while the persistence of other TNFis was lower in bDMARD-experienced AS and PsA patients who started TNFi therapy after 1 January 2010. This is also the first report on the subject in the oft-underrepresented Central European region.

Following a population of in total 368 patients, the persistence of golimumab after 2 years of treatment was 53%, 67%

Table 2 Univariate and multivariate Cox proportional hazards model for the persistence of golimumab and other TNF inhibitors by prior bDMARD exposure

	Golimumab HR (95% CI, *p*)		Other TNFi HR (95% CI, *p*)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Rheumatoid arthritis				
bDMARD naïve	0.90 (0.47–1.70, 0.760)	0.54 (0.26–1.16, 0.115)	0.87 (0.72–1.10, 0.170)	0.88 (0.72–1.07, 0.198)
Age	1.00 (0.99–1.00, 0.280)	1.01 (0.98–1.03, 0.646)	1.00 (1.00–1.00, 0.012)	1.01 (1.00–1.02, 0.072)
Females	4.20 (1.70–10.0, 0.002)	3.65 (1.41–9.45, 0.008)	1.00 (0.80–1.30, 0.890)	0.97 (0.76–1.23, 0.790)
Rheumatoid factor positive	0.60 (0.35–1.00, 0.071)	0.66 (0.38–1.18, 0.160)	0.98 (0.80–1.20, 0.890)	0.92 (0.75–1.15, 0.499)
ACPA positive	1.30 (0.69–2.50, 0.420)		0.99 (0.80–1.20, 0.960)	
Ever smokers	0.80 (0.44–1.50, 0.470)		1.20 (0.96–1.40, 0.140)	
DAS28ESR at baseline	1.40 (1.10–1.70, 0.005)	1.44 (1.11–1.86, 0.006)	1.10 (1.00–1.20, 0.035)	1.07 (0.99–1.16, 0.079)
Past csDMARD count	0.99 (0.74–1.30, 0.930)		0.97 (0.89–1.10, 0.450)	
Concomitant csDMARD	0.95 (0.52–1.70, 0.880)	0.94 (0.49–1.80, 0.841)	0.90 (0.74–1.10, 0.290)	0.91 (0.74–1.13, 0.42)
Concomitant glucocorticoid	1.60 (0.97–2.70, 0.067)	1.20 (0.67–2.16, 0.546)	1.50 (1.20–1.70, < 0.0001)	1.44 (1.20–1.74, 0.0001)
bDMARD treatment course	1.30 (0.79–2.20, 0.290)		0.90 (0.90–1.20, 0.610)	
Year of bDMARD initiation	0.91 (0.80–1.00, 0.160)	0.89 (0.76–1.03, 0.111)	1.00 (0.99–1.10, 0.170)	1.05 (1.00–1.10, 0.064)
Ankylosing spondylitis				
bDMARD naïve	0.80 (0.48–1.3, 0.410)	0.73 (0.43–1.24, 0.245)	0.53 (0.39–0.71, < 0.0001)	0.54 (0.39–0.74, 0.0001)
Age	1.00 (1.00–1.00, 0.072)	1.02 (1.00–1.04, 0.047)	1.00 (0.99–1.00, 0.730)	1.00 (0.99–1.01, 0.846)
Females	1.20 (0.71–2.00, 0.490)	1.10 (0.65–1.88, 0.679)	1.60 (1.20–2.10, 0.002)	1.57 (1.17–2.11, 0.003)
Ever smokers	1.40 (0.82–2.30, 0.230)		1.30 (0.96–1.70, 0.087)	
HLA-B27 positive	0.47 (0.25–0.88, 0.018)	0.49 (0.26–0.92, 0.026)	0.84 (0.58–1.20, 0.330)	0.90 (0.63–1.83, 0.555)
BASDAI	1.20 (1.00–1.40, 0.010)	1.19 (1.04–1.36, 0.009)	1.00 (0.97–1.10, 0.270)	1.07 (0.99–1.15, 0.089)
ASDAS-CRP	1.20 (1.00–1.60, 0.130)		1.00 (0.86–1.20, 0.970)	
Year of bDMARD initiation	1.10 (0.95–1.20, 0.230)	1.05 (0.92–1.20, 0.485)	1.00 (0.95–1.10, 0.440)	1.00 (0.92–1.09, 0.971)
Psoriatic arthritis				
bDMARD naïve	0.69 (0.36–1.30, 0.250)	0.66 (0.34–1.30, 0.230)	0.64 (0.46–0.89, 0.008)	0.68 (0.48–0.95, 0.026)
Age	1.00 (0.98–1.00, 0.790)	1.00 (0.97–1.03, 0.811)	1.00 (1.00–1.00, 0.013)	1.01 (1.00–1.03, 0.120)
Females	0.91 (0.50–1.70, 0.760)	0.68 (0.97–1.03, 0.262)	1.70 (1.20–2.30, 0.002)	1.59 (1.13–2.24, 0.008)
Ever smokers	1.80 (0.90–3.40, 0.096)		0.76 (0.50–1.20, 0.210)	
HLA-B27 positive	0.52 (0.22–1.20, 0.140)		0.79 (0.47–1.40, 0.400)	
DAS28ESR at baseline	1.20 (0.96–1.40, 0.130)	1.24 (0.99–1.56, 0.065)	1.10 (0.97–1.20, 0.130)	1.02 (0.90–1.16, 0.780)
Concomitant csDMARD	0.99 (0.53–1.80, 0.980)		0.76 (0.54–1.10, 0.100)	
bDMARD treatment course	1.00 (0.75–1.40, 0.810)		1.40 (1.10–1.60, < 0.0001)	
Year of bDMARD initiation	1.00 (0.88–1.20, 0.710)	0.98 (0.83–1.16, 0.824)	1.00 (0.92–1.10, 0.94)	0.99 (0.90–1.09, 0.853)

and 59% in patients with RA, AS and PsA, respectively. This was comparable to the 2-year persistence in the other TNFi-group of 47%, 65% and 59% and less than the reported 5-year retention rates in the extensions of the randomised clinical trials of 60%, 72% and 69% in RA, AS and PsA, respectively [6]. Our findings are closer to the contemporary observations of golimumab persistence in other real-world settings. Analyses of the Italian LORHEN registry revealed 2-year persistence rates of 47%, 63% and 48% for RA, axial-spondylarthritis and PsA, respectively [8]. The Italian GOAREL study showed 2-year persistence rates of 63.6%, 78.2% and 66.9% for RA, axial-spondylarthritis and PsA, respectively [9]. The Finnish ROB-FIN registry revealed 68% (95% CI 59–79%) 2-year persistence of golimumab in RA patients [12]. The data form Reuma.pt showed a 1-year persistence rate of 75.3% in patients with RA, which is higher than our observation of 66% [10]. The combined persistence analysis of golimumab in RA, AS or PsA from Sweden showed a 2-year persistence of 46% (95% CI 43–50%) [11]. While the real-world evidence invariably suggests a lower persistence of golimumab than the clinical trials, with some differences among the different registries, the lowest persistence was found in the LOHREN registry, which collects data from the eight tertiary centres in the affluent northern Italy, sharing its east boarder with Slovenia. This may be attributable to a more difficult-to-treat population in the tertiary

setting and a patient base with higher expectations. This assumption is indirectly supported by the results of the GOAREL study which included nine rheumatology centres in the less affluent Apulia region in the South of Italy, the data from the Reuma.pt. and our own observations.

Our study and several other studies included in the recent review [19] compared the persistence of golimumab between bDMARD-naïve and bDMARD-experienced patients and found no difference between these two groups. While we found no difference in the overall persistence of golimumab compared to other TNFis in AS and PsA, we observed a significantly lower persistence in bDMARD-experienced AS and PsA patients treated with other TNFis (Fig. 1, bottom two panels). This may be in part explained by a high acceptance of golimumab by the patients due to its long dosing interval, and in part by its low immunogenicity [20, 21].

In RA patients, these may not be the only reasons. Most of the TNFi cycling studies in RA patients suggested that the probability of achieving a response as well as the average magnitude of response is lower with each subsequent TNFi. However, most of these studies were done before golimumab and bDMARDs with alternative mode of action became available [22, 23]. Especially the availability of bDMARDs with alternative modes of action that led to a change in prescription habits which is reflected in a low count of TNFi-experienced patients in both golimumab- and other TNFi-treated patients in our cohort, which might have precluded us to detect the difference in persistence between bDMARD-naïve and bDMARD-experienced patients.

The evidence on the role of TNFi-cycling, which was until very recently the only option in AS and PsA patients who failed treatment with one of the TNFis, is not as extensive as in RA. We found only three larger studies examining TNFi-cycling in AS patients, of which only the DANBIO study included a small proportion of patients treated with golimumab. These studies suggested worse outcomes with each subsequent TNFi [24–26]. A recent systematic review of the literature examined the real-world effectiveness of TNFi-cycling in PsA patients. The conclusions were similar as in RA and AS cohorts: the treatment response diminishes with each subsequent TNFi. However, the lack of a common outcome measure in PsA precluded a systematic comparison of outcomes and any firm conclusions [27]. The available real-world evidence of TNFi-cycling in AS and PsA, mostly lacking data on the newer TNFis, e.g. golimumab and certolizumab, is in line with the observations from our other TNFi-group, where the persistence was significantly lower in the bDMARD-experienced patients. In contrast, the persistence in the golimumab-treated group did not differ between bDMARD-naïve and bDMARD-experienced patients. Of note, most of the bDMARD-experienced patients in both groups only failed a single TNFi. Combining these observations with the comparable 1-year effectiveness of the golimumab and TNFi treatments in our cohort and similar observations from other real-world studies [8, 9, 11] suggests that golimumab may have an advantage in TNFi-experienced, patients over other TNFis, at least after the patients fail a single TNFi.

Interestingly, using the multivariate Cox-models, we observed different baseline patient characteristics other than prior bDMARD exposure to be significantly associated with the persistence of golimumab compared to other TNFis (Table 2). In RA patients, persistence was significantly worse in females, and patients with a higher DAS28ESR at baseline in the golimumab group, and in the patients, who used glucocorticoids at baseline in the TNFi-group. The observation of the glucocorticoid therapy being adversely associated with RA treatment persistence is in line with that from the ROB-FIN [12]. In AS patients, the persistence was marginally adversely affected by the patients' age, significantly so by the higher baseline BASDAI, but not ASDAS-CRP, and better in HLA-B27 positive patients in the golimumab-treated group in contrast to other TNFi groups where we only found female sex to be associated with a lower persistence. In PsA patients, none of the considered baseline characteristics seemed to significantly influence the persistence of golimumab, while female sex adversely impacted the persistence in the other TNFi group.

Our study was subject to all the caveats related to the analyses of real-world registry data and was also hampered by the relatively few bDMARD-experienced patients. It must also be noted that we present data for ankylosing spondylitis, while the two Italian studies presented the persistence of golimumab in axial spondylarthritis. The major strong point of the study is the use of the mandatory, national, multicentric registry BioRx.si which means that data from almost all patients treated with bDMARDs in Slovenia for the included indications are recorded by the prescribing rheumatologists, except for the patients with PsA in whom bDMARDs might be initiated by their dermatologists for psoriasis. The other strong points being one of the longest follow-up periods among the studies examining the persistence of golimumab, a decent sized comparator other TNFi-group, adjustment of the persistence for known confounders in the Cox proportional hazards models and the provision of treatment effectiveness at 1 year to substantiate the meaningfulness of golimumab persistence.

In conclusion, the persistence of golimumab in patients with RA, AS and PsA in Slovenia was comparable with the persistence in more affluent Western European countries. The overall persistence of golimumab and other TNFi was comparable for studied indications. Notably, we observed no differences in the persistence between bDMARD-naïve and bDMARD-experienced patients treated with golimumab, regardless of the indication and a significantly lower persistence of other TNFis in bDMARD-experienced AS and PsA patients.

ACPA anti-citrullinated peptide antibodies, *ASDAS* ankylosing spondylitis disease activity score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *bDMARD* conventional disease-modifying anti-rheumatic drugs, *CRP* C-reactive protein, *csDMARD* conventional disease-modifying anti-rheumatic drugs, *DAS28ESR* Disease activity index based on 28 tender and swollen joint counts and erythrocyte sedimentation rate, *EGA* evaluator global disease activity assessment, *HAQ* health assessment questionnaire, *PGA* patient global disease activity assessment, *RF* rheumatoid factor

HR hazard ratio (HR < 1 favours persistence), *CI* confidence interval

Adjusted for bDMARD exposure, age, gender, baseline DAS28ESR, rheumatoid factor, concomitant use of conventional synthetic disease-modifying antirheumatic drugs at baseline and year of TNFi initiation

Adjusted for bDMARD exposure, age, gender, baseline BASDAI, HLA-B27 status

Adjusted for age, gender, baseline DAS28ESR and year of golimumab initiation

Acknowledgments We are very grateful to all Slovenian Rheumatologists who contributed data into the BioRx.si.

Funding The study was financially supported by MSD. MSD had no influence on the study design or manuscript preparation.

Compliance with ethical standards

Conflict of interest ZR has received speaker fees from Abbvie, CellGen, Celtrion, Eli-Lilly, Jansen, Medis, MSD, Novartis, Pfizer and Roche. SP has received consultant or speaker fees from Abbvie, Eli-Lilly, Jansen, MSD, Novartis, Pfizer, Roche. MT has received consultant or speaker fees from Abbvie, Eli-Lilly, Johnson & Johnson, Medis, MSD, Novartis, Pfizer and Roche paid to Revmatic d.o.o. BioRx.si has received funding for clinical research paid to Društvo za razvoj revmatologije from AbbVie, Celgene, Celtrion, Eli Lilly, Johnson & Johnson, Medis, MSD, Novartis, Pfizer and Roche.

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