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RESEARCH ARTICLE

Long-term retention of golimumab treatment in clinical practice in a large cohort of patients with rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis

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Abstract

Aim: To assess the golimumab retention rate during up to 8 years of follow up, and any associated factors.

Methods: Retrospective analysis of the BIOBADASER (Spanish registry of biological drugs) database, assessing all adults who had ever started golimumab >6 months before the analysis for an approved indication (rheumatoid arthritis [RA], axial spondyloarthritis [SpA] or psoriatic arthritis [PsA]).

Results: Among 885 patients (RA 267, axial SpA 370, PsA 248) receiving 944 cycles of golimumab, the retention rate of golimumab was 71.1% (95% confidence interval:

68.0–73.9) at year 1% and 37.7% (95% CI: 33.3–42.1) at year 7 and at year 8. Retention was higher when golimumab was used as the first biological drug (81.7% at year 1, 49.9% at year 7, $p < 0.001$). In Cox regression analysis, factors associated with golimumab retention included use as first-line therapy (hazard ratio [HR] for discontinuation 1.52 for second- and 1.79 for third/later-line vs. first-line), use in axial SpA or PsA rather than RA (HR for axial SpA vs. RA 0.59, for PsA vs. Rheumatoid arthritis 0.67), and treatment with concomitant methotrexate (HR 0.67). Factors associated with golimumab discontinuation were corticosteroid use (HR 1.46) and disease activity above median (HR 1.29) at golimumab initiation.

Conclusion: Based on this retrospective analysis of the BIOBADASER registry, nearly two-fifths (37.7%) of adult rheumatology patients initiating golimumab will remain on treatment for 8 years, with a higher probability of retention in axial SpA or PsA indications and when golimumab is used as first biologic.

KEYWORDS
axial spondyloarthritis, golimumab, psoriatic arthritis, rheumatoid arthritis, treatment retention

1 | INTRODUCTION

Biological disease-modifying antirheumatic drugs (bDMARDs) are an important option for the treatment of patients with immune-mediated rheumatic diseases, including rheumatoid arthritis (RA), axial spondyloarthritis (SpA), and psoriatic arthritis (PsA) (Gossec et al., 2020; Smolen et al., 2020; van der Heijde et al., 2017). Long-term persistence with treatment is needed to achieve the greatest benefit from bDMARDs; however, many patients discontinue treatment after receiving one or more lines of therapy (Dalén et al., 2016; Ebina et al., 2020). Retention tends to decrease with each subsequent line of therapy (Prior-Español et al., 2021; Svedbom, Dalén et al., 2017), and such changes are associated with increased healthcare costs (Carballo et al., 2021; Svedbom, Dalén et al., 2017). Therefore, treatment decisions should take into account the probability of persisting with the same bDMARDs over time.

Golimumab is a tumour necrosis factor inhibitor (TNFi) indicated for the treatment of RA, axial SpA and PsA that is administered subcutaneously using a once-monthly dosing interval (Tahir and Kavanaugh, 2018). In long-term extensions of clinical trials in biologic-naïve patients with RA, SpA or PsA, golimumab showed a high retention rate of around 70% after 5 years of follow-up (Deodhar et al., 2015; Emery et al., 2016; Keystone et al., 2016). Analyses of routine clinical practice data from the Spanish BIOBADASER registry of patients treated with biological therapies for rheumatic diseases found a golimumab retention rate of 57.1% at 5 years after treatment initiation (Hernandez et al., 2019), and 39.5% at 7 years (Pombo-Suarez et al., 2021), but with a limited sample size in several patient subgroups.

The current study is an updated analysis of the BIOBADASER registry to assess retention of golimumab during up to 8 years after treatment initiation in a larger sample of patients with RA, axial SpA, or PsA, and to explore factors associated with long-term golimumab retention.

2 | METHODS

This was a retrospective analysis of BIOBADASER, the Spanish registry of biological drugs. BIOBADASER is promoted by the Spanish Agency of Medicines (https://www.aemps.gob.es/en/home.htm) and the Spanish Society of Rheumatology (https://www.ser.es/). The registry currently involves investigators from 28 university hospitals, which are representative of the Spanish public healthcare system. Patients with rheumatic diseases are enroled when they start treatment with a biologic or targeted-synthetic DMARD and are followed up prospectively whilst they are being treated with these drugs until treatment discontinuation. The methodology and procedures of BIOBADASER have recently been updated and published elsewhere (Sanchez-Piedra et al., 2019).

Prior to inclusion in the BIOBADASER registry, all patients provide informed consent, which includes consent for subsequent analysis of anonymised aggregated data, such as the present study. As stated in that consent form, and as approved by the Clinical Research Committee, specific informed consent for this anonymised analysis was therefore not required.

The aim of this study was to assess the retention rate of golimumab during up to 8 years of follow up, and any associated factors. For this purpose, all adult patients registered in BIOBADASER who had ever started golimumab for an approved indication (RA, axial SpA or PsA), and had initiated it more than 6 months before the analysis date, were included. Data extraction took place in November 2021. Patients prescribed golimumab for conditions not stated in the label, or who started golimumab before adulthood, were excluded.

The primary objective of the current analysis was to assess the probability of long-term retention (drug survival or persistence) of golimumab treatment up to 8 years after treatment initiation. The secondary objectives were to assess the probability of retention of golimumab treatment by indication (RA, axial SpA or PsA) and by line of therapy (first, second, or third or later biological therapy), and to explore factors associated with drug retention (including demographic and disease-related variables).

Patients were considered to have retained golimumab if they were still on treatment with golimumab at the time of data analysis. Patients were considered to have discontinued golimumab if they had permanently stopped golimumab, or if they had temporarily discontinued it for a period longer than 90 days (Grace period). Covariates (demographic and disease-related variables) were collected to assess factors associated with long-term golimumab retention.

2.1 | Statistical analysis

Descriptive statistics are displayed as means with standard deviations (SDs), medians with interquartile ranges, or percentages when applicable. All retention analyses (overall, by indication, by line of therapy, and by selected co-variates) were assessed using Kaplan-Meier survival analysis, and differences in retention between different stratification groups were assessed with the log-rank test. Right-censoring was applied to those subjects who were still on treatment with golimumab at the time of data analysis (i.e. the event of golimumab discontinuation had not occurred). When patients received more than one cycle of golimumab (e.g., discontinuation of a first treatment with golimumab, then treatment with other therapies, and later initiation of a second treatment with golimumab), both cycles were included in the retention analysis. Factors associated with discontinuation of golimumab were identified using multivariable Cox regression analysis. Kaplan-Meier and multivariable Cox regression analyses were performed for the overall cohort as well as separately for each specific condition (RA, axial SpA, PsA), and hazard ratios (HRs) for discontinuation of golimumab, with 95% confidence intervals, were calculated. Disease activity was introduced in the models as above or below the median Disease Activity Score (DAS 28) for RA and PsA (Prevoo et al., 1995; Wells et al., 2009), or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score for axial SpA (Calin et al., 1994; Garrett et al., 1994). Statistical analyses were conducted using Stata (version 13.1). *p*-values <0.05 were considered statistically significant.

3 | RESULTS

A total of 885 patients were included, comprising 412 men (46.6%) and 473 women (53.5%), with a diagnosis of RA (n = 267), axial SpA (n = 370) or PsA (n = 248). At golimumab initiation, the mean (SD) age was 51.5 (12.7) years, and the median duration of disease was 7.6 (interquartile range 2.8–14.4) years. Rheumatoid factor was positive in 162 (62.8%) of RA patients and HLA-27 was positive in 266 (71.9%) of axial SpA patients. Other demographic and disease characteristics are summarised for the overall sample and by indication in Table 1.

The total number of cycles of golimumab treatment analysed (with a grace period of 3 months applied to identify two different cycles in the same patient) was 944 (286 RA, 396 axial SpA and 262 PsA). Golimumab was initiated as the first biological drug for 313 (33.2%) treatments, as the second for 303 (32.2%) and as the third or subsequent biologic drug for 328 (34.8%) treatments. The lines of biological treatment were, roughly, similar across the three indications (Table 2). Concomitant medications at golimumab initiation included methotrexate (32.3%), steroids (28.7%), leflunomide (13.4%) and sulfasalazine (5.7%) (Table 2).

The probability of golimumab retention since treatment initiation was 71.1% (95% confidence interval [CI]: 68.0–73.9) at year 1, 60.2% (56.9–63.3) at year 2, 54.3% (50.8–57.6) at year 3, 48.0% (44.5–51.4) at year 4, 43.9% (40.2–47.6) at year 5, 41.0% (37.1–44.9) at year 6%, and 37.7% (33.3–42.1) at year 7 and at year 8 (Figure 1).

In bivariate analysis, the probability of golimumab retention was higher when it was used as the first-line biological agent (log-rank $p < 0.001$, Figure 2a) and in patients with axial SpA or PsA compared to RA ($p < 0.001$, Figure 2b). As first-line, the retention rate (95% CI) was 81.7% (76.9–85.6) at year 1% and 49.9% (42.0–57.3) at year 7. As second biological drug, it was 69.9% (64.3–74.7) at year 1% and 35.0% (27.7–42.3) at year 8, and as third/further line, 61.9% (56.3–67.0) and 27.9% (20.9–35.4) respectively (Figure 2a). Retention rates at year 1 and year 8 were 77.2% (72.7–81.1) and 45.8% (39.4–52.1) in patients with axial SpA and 75.4% (69.7–80.2) and 39.9% (31.9–47.8) in PsA patients, but they were lower for RA patients: 58.6% (52.6–64.1) at year 1% and 24.6% (15.4–35.0) at year 8 (Figure 2b). For each disease, the retention rates were higher when golimumab was used as the first-line biological agent (log-rank $p < 0.001$ for RA, $p < 0.001$ for axial SpA and $p = 0.003$ for PsA) (Supplementary Figures S1–S3).

Regarding other covariates, the golimumab retention rates were lower in women, in elderly patients (>65 years), in patients who were using steroids at golimumab initiation (all comparisons, log-rank $p < 0.001$), and in patients with higher disease activity at baseline (DAS 28 > 4.3, $p = 0.011$ or BASDAI >5.8, $p = 0.027$). There were no differences in retention rates regarding body mass index, smoking habit, or co-medication with methotrexate or other DMARDs at golimumab initiation in the overall cohort.

Table 3 shows the results of the multivariate Cox regression analysis with HRs for discontinuation of golimumab. For the overall cohort, factors positively associated with long-term retention included using golimumab as first-line biological therapy compared to second- or third/later-line therapy (HR for discontinuation = 1.52 for second- and 1.79 for third/later-line of therapy vs. first-line therapy), having axial SpA or PsA rather than RA as background disease (HR for discontinuation with axial SpA vs. RA = 0.59, and with PsA vs. RA = 0.67), and concomitant therapy with methotrexate at golimumab initiation (HR = 0.79). Factors associated with golimumab

TABLE 1 General characteristics of patients at golimumab initiation

		Rheumatoid arthritis (*n* = 267)	Axial spondyloarthritis (*n* = 370)	Psoriatic arthritis (*n* = 248)	All (*n* = 885)[a]
Age	Years, mean (SD)	57.4 (12.2)	48.2 (12.3)	50.2 (11.6)	51.5 (12.7)
Gender	Male, *n* (%)	62 (23.2)	240 (64.9)	110 (44.4)	412 (46.6)
	Female, *n* (%)	205 (76.8)	130 (35.1)	138 (55.7)	473 (53.5)
Disease duration	Years, median (IQR)	8.5 (3.5–14.6)	7.3 (2.3–16.0)	7.1 (3.0–12.5)	7.6 (2.8–14.4)
Smoking habit	Never, *n* (%)	152 (56.9)	191 (51.6)	159 (64.1)	502 (56.7)
	Current, *n* (%)	51 (19.1)	113 (30.5)	47 (19.0)	211 (23.8)
	Past, *n* (%)	47 (17.6)	43 (11.6)	29 (11.7)	119 (13.5)
	Not available, *n* (%)	17 (6.4)	23 (6.2)	13 (5.2)	53 (6.0)
Body mass index	Normal weight, *n* (%)	77 (28.8)	89 (24.1)	60 (24.2)	226 (25.5)
	Overweight, *n* (%)	85 (31.8)	125 (33.8)	84 (33.9)	294 (33.2)
	Obesity, *n* (%)	62 (23.2)	84 (22.7)	62 (25.0)	208 (23.5)
	Not available, *n* (%)	43 (16.1)	72 (19.5)	42 (16.9)	157 (17.7)
Main comorbidities	Diabetes mellitus, *n* (%)	21 (7.9)	18 (4.9)	27 (10.9)	66 (7.5)
	Hypertension, *n* (%)	66 (24.7)	81 (21.9)	59 (23.8)	206 (23.3)
	Cardiovascular disease, *n* (%)	17 (6.4)	22 (6.0)	5 (2.0)	44 (5.0)
	Osteoporosis, *n* (%)	44 (16.5)	25 (6.8)	15 (6.1)	84 (9.5)
	Cancer, *n* (%)	11 (4.1)	7 (1.9)	6 (2.4)	24 (2.7)
Activity indexes	DAS 28 (median, IQR)	4.6 (3.5–5.4)	-	4.1 (3.0–5.0)	-
	BASDAI (median, IQR)	-	6.0 (4.5–7.3)	5.2 (3.0–6.7)	-

Abbreviations: BASDAI, Bath Ankylosing Spondyloarthritis Disease Activity Index; DAS, Disease Activity Score; IQR, interquartile range; SD, standard deviation.

[a]For patients who received more than one cycle of treatment with golimumab, only the baseline characteristics upon initiation of the first cycle are included.

TABLE 2 Lines of golimumab treatment and concomitant medication at golimumab initiation

	Rheumatoid arthritis (*n* = 286)	Axial spondyloarthritis (*n* = 396)	Psoriatic arthritis (*n* = 262)	All (*n* = 944)[a]
Golimumab treatment				
First line of therapy (*n*, %)	102 (35.7)	133 (33.6)	78 (29.8)	313 (33.2)
Second line of therapy (*n*, %)	84 (29.4)	121 (30.6)	98 (37.4)	303 (32.1)
Third or subsequent line of therapy (*n*, %)	100 (35.0)	142 (35.9)	86 (32.8)	328 (34.8)
Concomitant treatment at golimumab initiation				
Corticosteroids (*n*, %)	164 (57.3)	39 (9.9)	68 (26.0)	271 (28.7)
Methotrexate (*n*, %)	145 (50.7)	53 (13.4)	107 (40.8)	305 (32.3)
Leflunomide (*n*, %)	83 (29.0)	6 (1.5)	37 (14.1)	126 (13.4)
Sulfasalazine (*n*, %)	9 (3.2)	29 (7.3)	16 (6.1)	54 (5.7)

[a]Number of cycles of treatment with golimumab.

discontinuation included use of corticosteroids at golimumab initiation (HR = 1.46) and baseline disease activity indexes (DAS 28 or BASDAI) above the median (HR = 1.29). Although not significant, the model also identified female sex (HR = 1.23, $p = 0.063$) and older age (HR = 1.01 per year of increment, $p = 0.079$) as factors that may be associated with golimumab discontinuation.

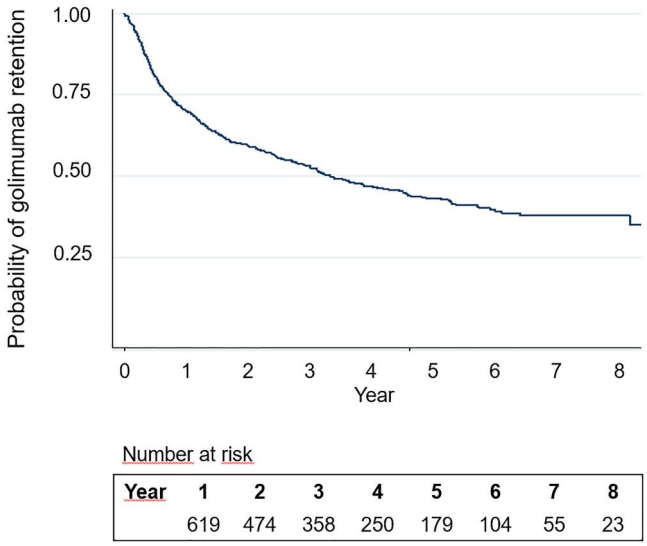

FIGURE 1 Probability of golimumab retention since treatment initiation for the overall cohort

Multivariable Cox regression models provided additional information on variables associated with the probability of golimumab retention for each specific indication (Table 4). In all models, use of golimumab as first-line biological therapy was associated with better golimumab retention. In RA, advanced age, treatment with steroids, and disease activity above the median at golimumab initiation were associated with a higher probability of golimumab discontinuation, whilst gender and Rheumatoid Factor were not. Although not statistically significant, Cox regression pointed to overweight ($p = 0.075$) and obesity ($p = 0.065$) as variables potentially associated with better retention of golimumab in RA. In axial SpA, female sex and BASDAI score above the median at golimumab initiation were associated with a higher probability of golimumab discontinuation, whilst age, HLA B27 status, and body mass index were not. In PsA, the only factor associated with golimumab discontinuation was its use as third-line therapy.

4 | DISCUSSION

Drug retention is a useful indicator of overall effectiveness in observational studies as it is affected by both efficacy and safety (González-Fernández et al., 2019). This analysis of data from routine clinical practice in Spain found a retention rate for golimumab treatment of 37.7% at year 8 after treatment initiation in patients with immune-mediated rheumatic disease (RA, axial SpA, and PsA).

These results update and extend those of previous analyses of the BIOBADSER registry (Hernandez et al., 2019; Pombo-Suarez et al., 2021). The current analysis included a larger sample of patients and a longer period of follow-up. The overall 5-year golimumab retention rate in the current study was 43.9%, compared with 45.1% and 57.1% in the earlier analyses (Hernandez et al., 2019; Pombo-Suarez et al., 2021). The 7-year retention rate was 39.5% in a

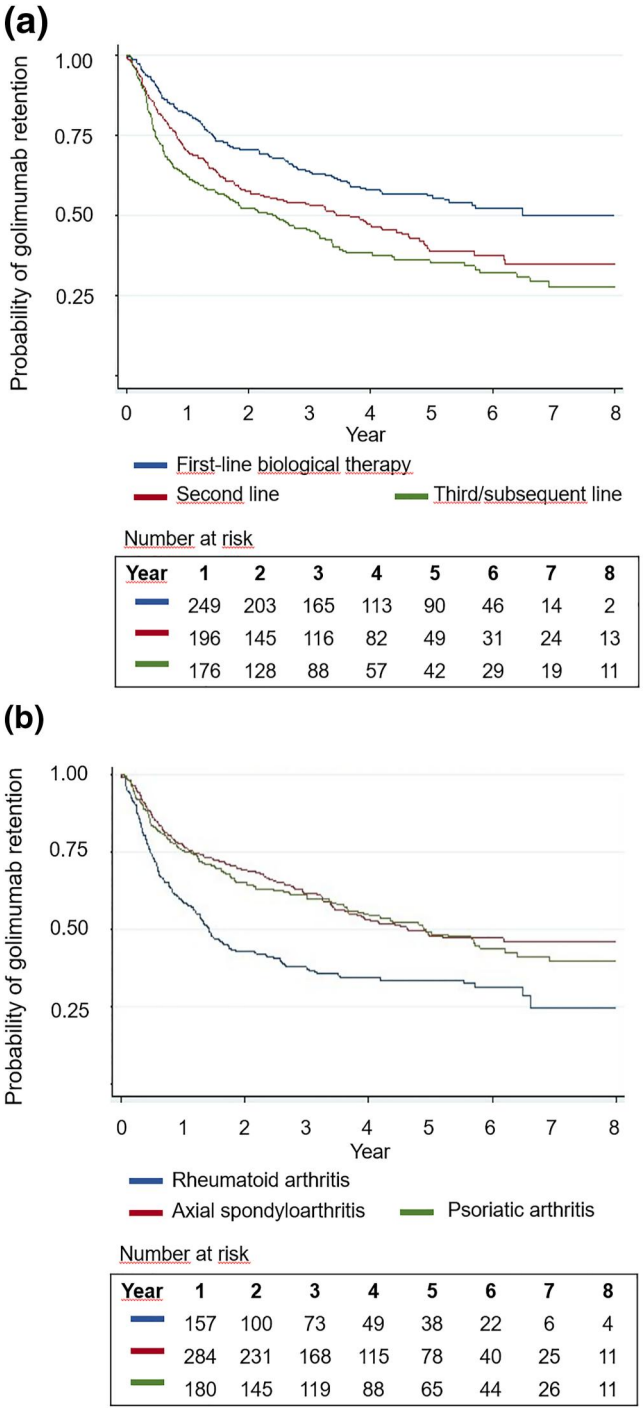

FIGURE 2 Probability of golimumab retention since treatment initiation (a) by line of therapy and (b) by indication

previous analysis of the registry (Pombo-Suarez et al., 2021);[14] the rate in the current analysis was similar, at 37.7%, and remained the same at year 8. Different studies have reported 3-, 4-, or 5-year retention rates for golimumab ranging from 35% to 65% (Aaltonen et al., 2017; Alegre-Sancho et al., 2021; Chimenti et al., 2022; Michelsen et al., 2020; Serrano_Benavente et al., 2022; Thomas et al., 2018), and a systematic review reported 3-year golimumab retention rates of 32%–67% (Svedbom, Storck et al., 2017). To the best of our knowledge, the

TABLE 3 Cox-regression analysis: Hazard ratios (HRs) for discontinuation of golimumab for the overall cohort

	Hazard ratio	95% confidence interval	*p*
Age at golimumab initiation	1.01	1.00–1.02	0.063
Gender (women vs. men)	1.23	0.98–1.55	0.079
Axial SpA versus RA	0.59	0.44–0.80	<0.001
PsA versus RA	0.67	0.51–0.89	0.005
Second versus first biological drug	1.52	1.17–1.97	0.002
Third or further versus first biological drug	1.79	1.38–2.32	<0.001
Corticosteroids	1.46	1.16–1.85	0.001
Methotrexate	0.79	0.63–0.99	0.041
Disease activity > median at golimumab initiation[a]	1.29	1.05–1.59	0.015

Abbreviations: BASDAI, Bath Ankylosing Spondyloarthritis Disease Activity Index; DAS, Disease Activity Score; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.
[a]DAS28 > 4.3 (RA), DAS28 > 4.2 (peripheral PsA) or BASDAI >5.8 (axial SpA, axial PsA) at golimumab initiation.

TABLE 4 Cox-regression analysis: Hazard ratios (HRs) for discontinuation of golimumab for each indication

	Hazard ratio	95% confidence interval	*p*
Rheumatoid arthritis			
Age at golimumab initiation	1.02	1.00–1.04	0.035
Overweight (vs. normal)	0.68	0.44–1.04	0.075
Obesity (vs. normal)	0.64	0.40–1.03	0.065
Second versus first biological drug	1.50	0.96–2.35	0.077
Third or further versus first biological drug	1.93	1.22–2.97	0.003
DAS 28 > median at golimumab initiation[a]	1.41	1.00–2.00	0.052
Methotrexate at golimumab initiation	0.83	0.57–1.17	0.293
Corticosteroids at golimumab initiation	1.79	1.24–2.57	0.002
Axial spondyloarthritis			
Gender (women vs. men)	1.53	1.11–2.11	0.009
Second versus first biological drug	1.63	1.10–2.41	0.014
Third or further versus first biological drug	1.63	1.09–2.43	0.016
BASDAI > median at golimumab initiation[a]	1.40	1.01–1.92	0.042
Psoriatic arthritis			
Gender (women vs. men)	1.35	(0.76–2.41	0.310
Second versus. first biological drug	1.49	(0.77–2.90)	0.238
Third versus first biological drug	2.63	(1.35–5.16)	0.005
Corticosteroids at golimumab initiation	1.47	(0.87–2.47)	0.149

Abbreviations: BASDAI, Bath Ankylosing Spondyloarthritis Disease Activity Index; DAS, Disease Activity Score; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.
[a]DAS28 > 4.3 (RA), DAS28 > 4.2 (peripheral PsA) or BASDAI > 5.8 (axial SpA, axial PsA) at golimumab initiation.

current analysis is the first to report on the golimumab retention rate during 8 years of follow-up in routine clinical practice in Spain.

Retention of golimumab (Hernandez et al., 2019; Pombo-Suarez et al., 2021) and other biological DMARDs (González-Fernández et al., 2019; Navarini et al., 2020; Prior-Español et al., 2021) appears to be greatest when they are used as first-line biological DMARD therapy, an observation which is consistent with our findings in the current analysis. The probability of retention at year 1 was 81.7%

when golimumab was administered as first-line therapy compared with 69.9% when it was given as second-line therapy. Retention rates were 49.9% at year 7 when given as first-line therapy and 35.0% at year 8 when given as second-line treatment. Multivariate Cox regression analysis confirmed that retention was greater when golimumab was used as first-line therapy compared with later lines. This was the case for the overall cohort and also for the three individual indications (RA, SpA and PsA).

The current analysis found that golimumab retention rates were higher among patients with axial SpA or PsA than in those with RA. This is consistent with a previous BIOBADASER analysis (Pombo-Suarez et al., 2021), and also with a Spanish study that evaluated a range of biological DMARDs and found that a higher percentage of SpA and PsA patients (51.6% and 59.7%) compared with RA patients (41.0%) continued with their first drug after a mean 3.8 years of follow-up (Cañete et al., 2020). Our findings also align with those from a recent analysis from the DANBIO cohort on 17,903 series of treatments with biologics or targeted synthetic DMARDs which described higher drug survival for golimumab in axial SpA compared to all other therapies, and a tendency towards higher survival in PsA, but not in RA (Egeberg et al., 2022).

Cox regression analysis also identified concomitant methotrexate at the time of golimumab initiation as being associated with improved long-term retention of golimumab. Clinical trials have previously shown that the combination of golimumab plus methotrexate is more efficacious than golimumab monotherapy (Keystone et al., 2009). Cox regression found that use of corticosteroids and above-median disease activity at baseline were associated with a reduced likelihood of golimumab retention. A need for corticosteroid therapy could be an indicator of more severe disease which could, in turn, increase the risk of treatment failure (Souto et al., 2016).

Non-persistence with biological DMARD therapy can have an impact on healthcare costs for patients with immune-mediated rheumatic diseases, with higher costs reported for patients who discontinue their treatment, as recently described in studies that compared patients who initiated a first subcutaneous TNFi according to whether they were persistent or non-persistent with treatment (Carballo et al., 2021; Dalén et al., 2020). These studies have shown that among biologic-naïve patients who start treatment with a subcutaneous TNFi for immune-mediated rheumatic diseases, healthcare resource utilisation is greater among those who switch or discontinue therapy compared with those who persist with their first-line treatment (Carballo et al., 2021; Dalén et al., 2020). Thus, there is evidence that prescribing a TNFi with the greatest probability of persistence may be a cost-effective strategy (Svedbom et al., 2020).

Our study has several limitations derived from the registry design, including a lack of information on the use of golimumab dose escalation or tapering strategies, on concomitant medications other than at the time of golimumab initiation, and on some other potential confounding factors that could affect persistence with treatment. Strengths of the study include the use of data collected in routine clinical practice, which reflects the effectiveness of treatment in the broad population of patients seen in daily practice rather than in the carefully selected population evaluated in clinical trials. Another strength is the long period of follow-up of 8 years. The current study did not compare golimumab retention rates with those of other TNFi drugs. However, multiple previous studies in a clinical practice setting suggest that golimumab retention rates are as good as, or better than, those seen with other TNFi drugs in patients with immune-mediated rheumatic diseases (Dalén et al., 2016; Ebina et al., 2019; Egeberg et al., 2022; Kim et al., 2021; Svedbom, Storck et al., 2017).

In conclusion, this retrospective analysis of the BIOBADASER registry suggests that about two-fifths (37.7%) of adult patients with immune-mediated rheumatic diseases (RA, axial SpA, or PsA) who initiate golimumab in routine clinical practice will remain on treatment for 8 years. Factors positively associated with long-term golimumab retention included its use as first-line biological therapy, treatment of axial SpA or PsA (compared to RA), and concomitant treatment with methotrexate. Factors associated with higher rates of golimumab discontinuation included corticosteroid use and baseline disease activity above the median.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception, design, data collection and analysis of the results. The first draught of the manuscript was written by Luis Cea-Calvo, Daniel Seoane-Mato and Federico Díaz-González, and all other authors made substantial contributions and approved the final version.

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CONFLICT OF INTEREST

Manuel Pombo-Suárez: consulting honorarium from Janssen, MSD and Sanofi; lectures for Janssen, MSD and Novartis. Daniel Seoane-Mato: no conflict of interest. Federico Díaz-González: no conflict of interest. Luis Cea-Calvo: full-time employee at MSD, Spain. Fernando Sánchez-Alonso: no conflict of interest. Marta Sánchez-Jareño: full-time employee at MSD, Spain. Vega Jovani: no conflict of interest. Blanca García-Magallón: lectures for Janssen, Amgen and Pfizer; meeting expenses from Amgen & Pfizer. Olga Martínez-González: no conflict of interest. Cristina Campos-Fernández: no conflict of interest. Javier Manero: no conflict of interest. Cesar Díaz-Torne: lectures for Pfizer, Sanofi, Lilly, MSD and Galapagos. Cristina Bohórquez: no conflict of interest. Inmaculada Ros-Vilamajó: no conflict of interest. Yanira Pérez-Vera: no conflict of interest. Isabel Castrejón: no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was conducted according to Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All patients provide informed consent for BIOBADASER, which covers subsequent analysis of anonymized aggregated data like the present.

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SUPPORTING INFORMATION

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