



Factors associated with long-term retention of treatment with golimumab in a real-world setting: an analysis of the Spanish BIOBADASER registry

Maria V. Hernandez¹ · Carlos Sanchez-Piedra² · Blanca Garcia-Magallon³ · Eduardo Cuende⁴ · Javier Manero⁵ · Cristina Campos-Fernandez⁶ · Raquel Martin-Domenech⁷ · Javier del Pino-Montes⁸ · Sara Manrique⁹ · Maria C. Castro-Villegas¹⁰ · Dolores Ruiz-Montesinos¹¹ · Fernando Sanchez-Alonso² · Federico Diaz-Gonzalez¹² · Luis Cea-Calvo¹³ · Juan J. Gómez-Reino¹⁴ · On behalf of the BIOBADASER Study Group

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Abstract

The retention rate of a biological drug (percentage of patients remaining on treatment over time) provides an index of a drug's overall effectiveness. The golimumab retention rate as first-line biological therapy was high in clinical trial extensions lasting 5 years. Real-world studies also indicate good retention rates but have been of shorter duration. The probability of retention with golimumab treatment was assessed, as any line of anti-tumor necrosis factor-alpha therapy, for up to 5 years in patients with rheumatoid arthritis (RA), axial spondyloarthritis (SpA) or psoriatic arthritis (PsA), associated factors were analyzed. A retrospective database analysis of the Spanish registry of patients with rheumatic disorders receiving biological drugs (BIOBADASER) was performed. Among 353 patients, 29.8% had RA, 41.6% SpA and 28.6% PsA. Golimumab was the first biological drug in 40.1% of patients, second in 30.1% and third/later in 29.8%. The overall probability of retention of golimumab at years 1, 2, 3, 4 and 5 was 85.9% (95% confidence interval 81.4–89.5%), 73.7% (67.1–79.1%), 68.5% (60.5–75.1%), 60.6% (50.2–69.5%) and 57.1% (44.9–67.5%), respectively. Retention was similar across indications ($p=0.070$) but was greater when golimumab was used as the first biological agent compared with later therapy lines ($p<0.001$). Factors associated with higher retention of golimumab treatment (Cox regression) were use as a first-line biological and concomitant methotrexate treatment; corticosteroid need was associated with lower retention. The long-term probability of golimumab retention was high in this real-world study of patients with rheumatic diseases, especially when used as the first biological drug.

Keywords Ankylosing spondylitis · Axial spondyloarthritis · Golimumab · Medication retention rate · Psoriatic arthritis · Rheumatoid arthritis

✉ Juan J. Gómez-Reino
Juan.Jesus.Gomez-Reino.Carnota@sergas.es

¹ Rheumatology Service, Hospital Clinic i Provincial, Barcelona, Spain

² Research Unit, Sociedad Española de Reumatología, Madrid, Spain

³ Rheumatology Service, Hospital San Jorge, Huesca, Spain

⁴ Rheumatology Service, Hospital Universitario Príncipe de Asturias (Alcalá de Henares), Madrid, Spain

⁵ Rheumatology Service, Hospital Miguel Servet, Zaragoza, Spain

⁶ Rheumatology Service, Hospital General Universitario Valencia, Valencia, Spain

⁷ Rheumatology Service, Hospital de Elda, Alicante, Spain

⁸ Rheumatology Service, Hospital de Salamanca, Salamanca, Spain

⁹ Rheumatology Service, Hospital Carlos Haya de Málaga, Málaga, Spain

¹⁰ Rheumatology Service, Hospital Reina Sofía (Córdoba), Córdoba, Spain

¹¹ Rheumatology Service, Hospital Virgen de Macarena (Sevilla), Seville, Spain

¹² Rheumatology Service, Hospital Universitario de Canarias, San Cristóbal de La Laguna, Spain

¹³ Medical Affairs, Department, Merck Sharp and Dohme of Spain, Madrid, Spain

¹⁴ Rheumatology Department, Hospital Universitario de Santiago de Compostela, C/ Choupana s/n, 15701 Santiago de Compostela, Spain

Introduction

Biological disease-modifying antirheumatic drugs (bDMARDs) have improved the treatment of patients with immune-mediated rheumatic disorders, with tumor necrosis factor-alpha (TNF α) inhibitors being the most widely prescribed class of bDMARD for this patient population. Patients need to maintain long-term treatment to continue benefitting from the improvements achieved with these drugs. However, it has been reported that, after 4 years, up to 50% of patients discontinue treatment [1], generally because of a lack of efficacy, but also because of adverse events or personal preference [2].

The retention rate of treatment with biological therapy, or the probability of treatment persistence with the same biological drug (i.e. the probability of maintaining the treatment over time) provides an index of overall drug effectiveness, patient satisfaction and treatment compliance [3, 4]. Patients with rheumatic diseases who need to switch to another drug can incur higher healthcare-related costs [5]. It has been shown that persistence with a first TNF α inhibitor is greater than with a second TNF α inhibitor in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA), and that patients treated with a second TNF α inhibitor incur higher costs than those receiving their first TNF α inhibitor [6]. This highlights the importance of maintaining treatment with the same TNF α inhibitor from both clinical and healthcare cost perspectives.

Golimumab is a human anti-TNF α monoclonal antibody with high binding affinity for both soluble and transmembrane TNF [7]. It improves the signs and symptoms of disease in patients with RA, axial spondyloarthritis (SpA; including non-radiographic SpA and ankylosing spondylitis) or PsA [7]. In phase III trials, the golimumab retention rate was high among patients who received it as first-line biological therapy, with approximately 70% of recipients remaining on golimumab after 5 years [8–10]. In patients with RA who had experienced failure on other anti-TNF α agents, the 5-year retention rate for golimumab was approximately 40% [11]. Studies in a real-world setting have also indicated a high probability of persistence with golimumab treatment in patients with RA, axial SpA or PsA, with 3-year retention rates generally around 60% when it was used as the first biological drug and 50–60% when it was given as second-line biological treatment [12, 13].

The BIOBADASER registry, which was established in 2001, collects long-term follow-up data on patients with rheumatic disorders being treated with biological drugs in a real-world setting in Spain [14]. The database provides an opportunity to evaluate real-life, long-term persistence with antirheumatic treatments among patients with

immune-mediated rheumatic disorders. The objective of the current study was to assess the probability of retention with golimumab treatment for up to 5 years after treatment initiation in patients with RA, axial SpA or PsA who received it as any line of anti-TNF α therapy, and to identify factors associated with greater retention rate, using data from the BIOBADASER registry.

Methods

This was a retrospective noninterventional study, involving a database analysis of BIOBADASER, which focused on the long-term retention rate of golimumab therapy. BIOBADASER involves investigators from 35 university hospitals representative of the Spanish healthcare system. Patients are enrolled when they initiate a biological therapy and are followed up prospectively until treatment discontinuation. The registry is supported by the Spanish Agency of Medicines (<https://www.aemps.gob.es/en/home.htm>) and the Spanish Society of Rheumatology (<https://www.ser.es/>).

Patients

The present study included all adult patients from participating centers who had ever been treated with golimumab for an approved indication (RA, axial SpA including non-radiographic axial SpA and ankylosing spondylitis, or PsA) and had initiated it more than 6 months before the analysis date. Data extraction occurred in October 2017. All patients had signed informed consent to be included in the BIOBADASER registry, covering subsequent analysis such as the present analysis. Patients' information was managed as anonymized aggregated data and, as approved by the Clinical Research Committee, specific informed consent for this analysis was not required.

Outcome variables

The primary objective of this analysis was to assess the probability of retention with golimumab treatment up to 5 years after treatment initiation. The main variables were treatment start date (the date golimumab was administered for the first time after prescription) and treatment discontinuation date (the date golimumab was definitively stopped). Patients who stopped golimumab and resumed it after more than 90 days were counted as permanent discontinuations. Secondary objectives were to assess the probability of golimumab retention by disease type (RA, axial SpA and PsA) and by line of biological therapy (first, second, or third or later), and to explore potential factors associated with retention (including demographic and disease-related variables).

Procedures

Data were obtained retrospectively from the BIOBA-DASER database for all patients for the period from first golimumab prescription until permanent golimumab discontinuation (or last observation for those remaining on treatment). Data collection did not affect the treatment administered to patients. The study was approved by the reference committee and performed in accordance with Good Pharmacoepidemiology Practice standards and the principles of the Declaration of Helsinki. An aggregated report was obtained for this analysis, with no individualized data; consequently, specific informed consent for this study was not required.

Statistical analysis

Summary descriptive statistics were presented as means with standard deviations, medians with percentiles and percentages when applicable. The probability of retention of golimumab treatment was assessed using Kaplan–Meier survival analysis. Patients were right-censored if data were not available for a specific timepoint and for patients remaining on treatment at the time of data analysis. Kaplan–Meier analyses were performed for each specific disease (RA, axial SpA, PsA) and line of golimumab therapy (first, second, or third or later line of biological therapy). Differences according to indication and line of treatment were evaluated using the log-rank test. Cox regression analysis was performed to identify factors associated with golimumab discontinuation. Factors included in the Cox regression were background disease, line of therapy, co-medication and other factors described in previous literature as potential influencers of response to TNF α inhibitors, namely gender, smoking status or weight [15–17].

Results

At the time of data extraction, 353 patients (mean age 52.2 years) fulfilled the inclusion criteria [162 men (45.9%) and 191 women (54.1%)]. The main patient demographic and disease characteristics are summarized in Table 1. The indication for golimumab was RA for 105 patients (29.8%), axial SpA for 147 (41.6%) and PsA for 101 (28.6%). Median duration of disease at the onset of golimumab treatment was 8.0 (interquartile range 2.8–15.0) years. Golimumab was the first biological drug in 40.1% of patients, second in 30.1% and third or later biological drug in 29.8%. Overall, the most common concomitant medications at the time of golimumab initiation were methotrexate (33.7%) and steroids (26.0%).

Percentages for specific background disease are shown in Table 1.

The overall probability of retention of golimumab since treatment initiation was 85.9% (95% confidence interval 81.4–89.5%) at year 1, 73.7% (67.1–79.1%) at year 2, 68.5% (60.5–75.1%) at year 3, 60.6% (50.2–69.5%) at year 4 and 57.1% (44.9–67.5%) at year 5.

Retention of golimumab was similar for patients with RA, axial SpA or PsA (log-rank $p=0.070$, Fig. 1). For RA, the probability of retention at years 1, 2 and 3 was 81.8%, 62.4% and 58.3%, respectively; patient numbers at year 4 or later were too small to estimate probability. For patients with axial SpA, the probability of retention was 87.5% (year 1), 76.1% (year 2), 70.2% (year 3), 56.0% (year 4) and 48.0% (year 5), whilst it was 87.6% (year 1), 80.1% (year 2), 75.6% (year 3) and 70.6% (year 4) for PsA patients.

The rate of retention with golimumab therapy was greater when it was used as the first biological agent than when it was used as the second or third (or later) biological drug (log-rank $p<0.001$, Fig. 2). When used as the first biological drug, the probability of retention was 94.5% (year 1) and 85.4% (year 2); there were insufficient cases for assessment at year 3 or beyond. When used as the second biological drug, the probability of retention was 89.8% (year 1), 75.2% (year 2), 67.4% (year 3) and 59.2% (year 4). The values were 69.6%, 58.4%, 54.5% and 46.1%, respectively, when golimumab was used as third-line/late biological therapy.

Results from the Cox regression analysis to identify factors associated with retention of golimumab are shown in Table 2. The probability of retaining golimumab therapy was greater in patients who received it as first-line biological therapy rather than second- or third-line/late biological therapy (hazard ratio for discontinuation with second-line vs first-line therapy 2.30, 95% CI 1.16–4.55, and for third-line vs first-line therapy 3.92, 95% CI 2.07–7.39), and in those receiving concomitant methotrexate (HR for discontinuation 0.55, 95% CI 0.33–0.91). The probability was lower in those needing concomitant steroids (HR for discontinuation 2.83, 95% CI 1.72–4.66). The rate of golimumab retention seemed to be slightly lower in patients with RA compared with axial SpA or PsA but did not reach statistical significance.

Discussion

This registry analysis found that the overall probability of retention of golimumab treatment for patients with RA, axial SpA or PsA in a real-world setting was high in the short term (approximately 86% after 1 year) as well as in the long term, with an overall retention rate of up to 57% after 5 years of treatment initiation. Retention rates did not differ significantly between the different indications but were higher

Table 1 General characteristics of patients at golimumab initiation

	All (N=353)	Rheumatoid arthritis (N=105)	Axial spondyloarthritis (N=147)	Psoriatic arthritis (N=101)
Age				
Years, mean (SD)	52.2 (11.0)	57.2 (11.2)	49.8 (11.5)	50.4 (11.8)
Gender				
Male, n (%)	162 (45.9)	23 (21.9)	98 (66.7)	41 (40.6)
Female, n (%)	191 (54.1)	82 (78.1)	49 (33.3)	60 (59.4)
Duration of disease				
Years, median (IQR)	8.0 (2.8–15.0)	7.1 (2.7–12.9)	8.9 (3.2–19.4)	7.1 (2.8–11.6)
Smoking habit				
Never, n (%)	194 (55.0)	49 (46.7)	76 (51.7)	69 (68.3)
Current, n (%)	81 (23.0)	21 (20.0)	46 (31.3)	14 (13.9)
Past, n (%)	37 (10.5)	18 (17.1)	10 (6.8)	9 (8.9)
Not available, n (%)	41 (11.6)	17 (16.2)	15 (10.2)	9 (8.9)
Body mass index				
Normal weight	75 (21.2)	28 (26.7)	27 (18.4)	20 (19.8)
Overweight	120 (34.0)	24 (22.9)	61 (41.5)	35 (34.7)
Obesity	74 (21.0)	23 (21.9)	30 (20.4)	21 (20.8)
Not available, n (%)	84 (23.8)	30 (28.6)	29 (19.7)	25 (24.7)
Order of golimumab treatment^a				
First biological, n (%)	145 (40.1)	57 (52.8)	47 (31.3)	41 (39.4)
Second, n (%)	109 (30.1)	24 (22.2)	52 (34.7)	33 (31.7)
Third or later, n (%)	108 (29.8)	27 (25.0)	51 (34.0)	30 (28.9)
Concomitant medication				
Steroids, n (%)	94 (26.0)	54 (50.0)	19 (12.7)	21 (20.2)
Methotrexate, n (%)	122 (33.7)	59 (54.6)	22 (14.7)	41 (39.4)
Sulfasalazine, n (%)	22 (6.1)	2 (1.9)	15 (10.0)	5 (4.8)
Leflunomide, n (%)	46 (12.7)	27 (25.0)	4 (2.7)	15 (14.4)

IQR interquartile range, SD standard deviation

^aNine patients received two different golimumab treatments during follow-up

when golimumab was used as the first biological agent rather than as a later line of biological treatment.

The high level of golimumab retention seen in the BIOBADASER registry is consistent with previous data. Other real-world studies have shown high persistence with golimumab therapy over time, although they were limited by a shorter follow-up or were restricted to one specific disease [12, 13, 18, 19]. Overall, across all indications and lines of therapy, 3-year retention rates were 32–67% in these studies, with the lowest rates generally reported for third or later lines of biological treatment [12]. In the current study, golimumab retention at 3 years was 68.5% and, although findings are limited by lower patient numbers, data suggest a high retention rate also at years 4 and 5, which has not been described previously for golimumab in routine clinical practice.

Real-world studies complement the information provided by clinical trials [12, 20]. In long-term extensions of golimumab clinical trials, the 5-year retention rate on the drug

was approximately 70% when it was administered as first-line biological therapy in patients with RA, axial SpA or PsA, and 40% when given after failure of other TNF α inhibitors in RA patients [8–11]. The current registry study was only able to estimate retention rates up to year 2 for first-line use (85.4%), but the results appear to be consistent with the clinical trial findings.

The current analysis did not include a comparison with other TNF α inhibitors. However, other real-world studies have suggested that retention is at least as good, and possibly better, with golimumab than with some other TNF α inhibitors over 3 years [5, 21]. Low immunogenicity, good tolerability with a very low percentage of injection-related side effects and ease of use (1-month dosing and easy-to-use device) can account for better patient acceptance of the drug and, ultimately, high golimumab retention rates [22]. In the current study, regression analysis confirmed that the probability of continuing treatment with golimumab was higher when it was used as the first biological agent rather

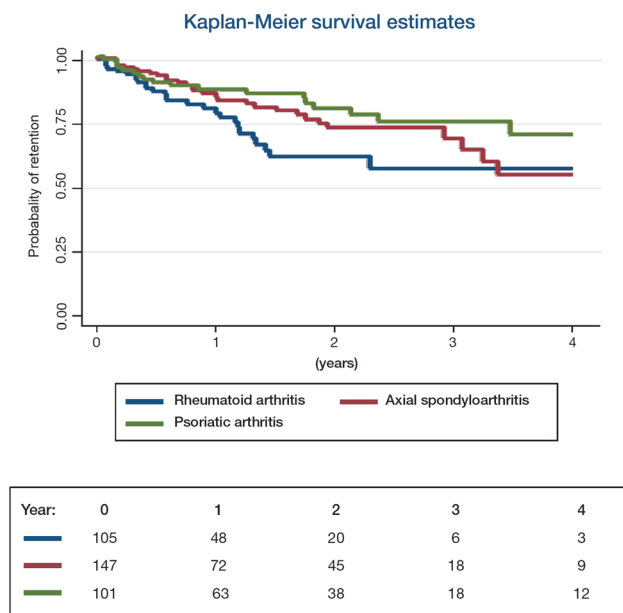


Fig. 1 Rate of retention of treatment with golimumab according to the underlying rheumatic disease (log-rank $p=0.070$)

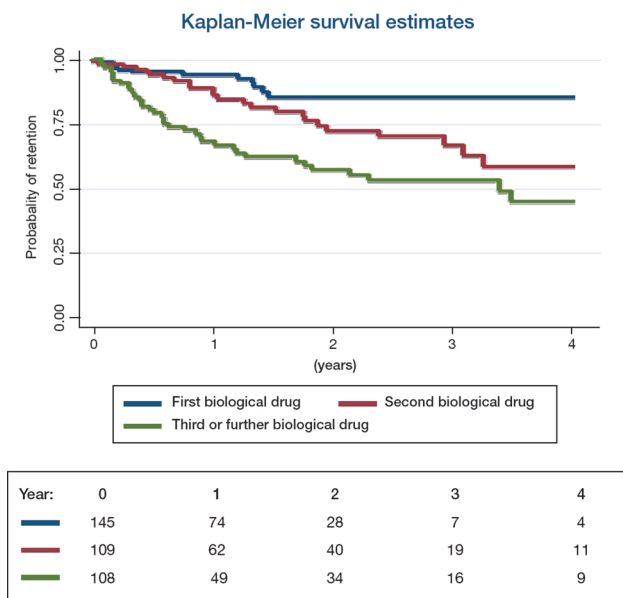


Fig. 2 Rate of retention of treatment with golimumab according to treatment line (log-rank $p<0.001$)

than as second- or third-line/late biological therapy. This is consistent with data reported previously for golimumab and other TNF α inhibitors [11, 12, 23]. Golimumab retention was better in patients who were receiving concomitant methotrexate. This has been reported previously for golimumab and other anti-TNF α agents in RA patients, and probably relates to a synergistic effect associated with a reduction in the immunogenicity of anti-TNF α monoclonal

Table 2 Factors associated with the retention of treatment with golimumab: hazard ratios for risk of discontinuation of golimumab (Cox regression analysis)

	Hazard ratio	95% confidence interval	p
Initial model			
Gender (women vs men)	1.23	0.62–2.44	0.56
Age at golimumab initiation	1.01	0.99–1.04	0.25
Disease duration	0.99	0.96–1.02	0.38
Smoking habit (vs non-smoker)	1.67	0.85–3.26	0.13
Overweight (vs normal)	1.61	0.74–3.52	0.23
Obesity (vs normal)	1.53	0.64–3.66	0.33
Second vs first biological drug	3.06	1.28–7.32	0.01
Third vs first biological drug	5.22	2.18–12.49	<0.01
Axial SpA vs RA	0.79	0.36–1.73	0.55
PsA vs RA	0.59	0.27–1.29	0.19
Methotrexate	0.41	0.21–0.80	0.01
Steroids	4.26	2.26–8.04	<0.01
Final model			
Gender (women vs men)	1.38	0.84–2.27	0.21
Age at golimumab initiation	1.01	1.00–1.03	0.14
Second vs first biological drug	2.30	1.16–4.55	0.02
Third vs first biological drug	3.92	2.07–7.39	<0.01
Methotrexate	0.55	0.33–0.91	0.02
Steroids	2.83	1.72–4.66	<0.01

PsA psoriatic arthritis, RA rheumatoid arthritis, SpA spondyloarthritis

antibodies [1, 21, 24]. Finally, golimumab retention was reduced in patients who were receiving concomitant steroids, which is consistent with other reports that suggest a need for steroids may be a marker of increased risk of future treatment failure [1]. With regard to other potential factors, smoking habit, body mass index and diagnosis were not associated with golimumab retention rate in the Cox regression model. However, several studies suggest that smoking habit [17] and being overweight or obese [15, 16] can reduce the response to anti-TNF α agents. Failure to find these associations in our study can be explained, in part, by the limited sample size.

In conclusion, long-term retention of treatment with golimumab was high in this real-world study of patients with RA, axial SpA or PsA. Factors associated with an increased probability of retaining golimumab treatment included use as first-line biological therapy and concomitant methotrexate treatment, while steroid need was associated with reduced retention. We cannot rule out the influence of other factors; this aspect requires a larger study to be conducted.

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Author contributions MVH, CS-P, FD-G, LC-C and JJG-R were involved in the design of the study. Statistical analysis was independently executed by CS-P and FD-G, with overview from MVH, and interpretation by the abovementioned authors. LC-C, an employee of MSD Spain, was involved in the design of the study but was not involved in data collection and had no access to the data source. The rest of the authors are regular investigators of BIOBADASER and made contributions to the current work. All authors reviewed and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest L Cea-Calvo is an employee of Merck Sharp & Dohme, Spain. The other authors declare no conflict of interest in relation to this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All patients signed informed consent to be included in the BIOBADASER registry. Informed consent included consent for subsequent analysis, such as in the present analysis. Patients' information was managed as anonymized aggregated data and, as approved by the Clinical Research Committee, specific informed consent for this analysis was not required.

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