Two-year retention rate of golimumab in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: data from the LORHEN registry

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Abstract

Objective

We aimed to provide data on golimumab real-life use in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) from a multicentre observational registry of Northern Italy.

Methods

We extracted data of patients who started treatment with golimumab from October 2010, and who had at least one follow-up visit. Data were analysed until a maximum follow-up of 24 months. The two-year retention rate in the three diseases was assessed with Kaplan-Meier estimators. To compare crude survival between diagnoses and lines of treatment we used the log-rank test, while Cox proportional hazard models were used to adjust for confounders.

Results

Overall, 410 subjects were included: 180 patients with RA, 110 with PsA and 120 with AS. The two-year retention rate of patients with RA was 47.3%, 48% for PsA, and 62.8% for AS. Crude survival on treatment of patients with AS was significantly higher than that of RA patients (p=0.032), while no significant difference was found between AS and PsA and between RA and PsA. In patients with RA, subjects treated with concomitant sDMARDs showed a lower discontinuation rate than those receiving golimumab alone. The comparison between first and second line of treatment groups did not show any significant difference in mean survival time in patients with RA, PsA and AS.

Conclusion

This is the first report of real-life data on two-year survival on treatment with golimumab in RA, PsA and AS. Golimumab showed a similar retention rate when given as first or second line of treatment.

Key words

golimumab, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, retention rate

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Introduction

The disease course of inflammatory arthritis has dramatically been changed by the introduction of biologic disease modifying anti-rheumatic drugs (bDMARDs) in the therapeutic arsenal. The first biologic drugs licensed for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) were directed against tumour necrosis factor α (TNF) and their efficacy was demonstrated in various clinical trials.

Golimumab is a human monoclonal antibody specifically targeting human TNF (1). Its high affinity for human TNF and its relatively low immunogenicity ensure a long half-life *in vivo*, so that it was the first anti-TNF drug with a once-monthly subcutaneous administration to be approved for the treatment of RA, PsA and AS (2).

A number of randomised clinical trials (RCTs) demonstrated the efficacy of golimumab in the treatment of RA, PsA and AS in terms of reducing disease activity, inhibiting radiographic progression and preventing disability (3-8). In these trials golimumab was administered alone or in combination with methotrexate, with a good safety profile (9, 10).

However, data from RCTs generally lack of external validity because of stringent inclusion and exclusion criteria, and only real-life observations can provide indications on long-term effectiveness and safety in clinical settings. To date, real-life data on golimumab are scarce. On this basis, the aim of this study was to provide data on golimumab real-life use from a multicentre observational registry of Northern Italy.

Methods

The LORHEN registry

The data of the patients included in this study were extracted from the LORHEN registry, previously described in detail elsewhere (11). In brief, LORHEN is a regional multicentre population-based registry established in 1999 with the aim of collecting demographic and clinical data of all the patients with RA, PsA or AS and age ≥18 years, treated with bDMARDs in eight tertiary Rheumatology Centres of Northern Italy. Subjects enter the registry when starting their first treatment with a biological agent and they are followed in time until treatment discontinuation. If patients switch to another biological therapy, they are followed in the registry throughout the course of the treatment. Biological agents are prescribed in accordance with good clinical practice in patients with moderate-to-severe disease who failed previous treatments with synthetic DMARDs (sDMARDs) (or NSAIDs for patients with AS).

At baseline data are collected regarding demographic characteristics of the patient, diagnosis and date of diagnosis, previous and current treatments with synthetic or biological DMARDs and symptomatic drugs. For patients with RA, rheumatoid factor and anti-citrullinated antibodies positivity is recorded, as well as clinical subtype for patients with PsA.

Disease activity and severity indices are collected at baseline and follow-up visits at least every 6 months, and at the end of treatment in cases of discontinuation. Treatment modifications and adverse events are assessed at each visit. Date and reason for eventual drug discontinuation are recorded systematically.

Data analysis

For the present study we extracted data of patients affected by RA, PsA or AS, who started treatment with golimumab from October 2010, and who had at least one follow-up visit. Golimumab was given at the dosage of 50 mg every 4 weeks subcutaneously. Data up to November 30th, 2015 were used for the analysis.

The primary outcome of the study was to assess the two-year retention rate of the treatment with golimumab in the three diseases. Treatment duration was assessed as the time between the first administration of the drug and the last day of the treatment, or the last available follow-up visit. The data were analysed up to a maximum follow-up of 24 months. Patients who discontinued bDMARDs because of pregnancy or inactive disease/remission were censored at the date of withdrawal and thus not counted as events in the survival analysis.

Secondary outcomes of the study were to compare the different persistence with the treatment related to patients' diagnosis, and to explore reasons for discontinuation (inefficacy, that means primary or secondary lack of response according to clinical judgement, or adverse events). Discontinuation rates were also adjusted for age, sex and disease duration.

In patients with the same diagnosis, we explored the effect of concomitant treatment with sDMARDs (methotrexate, leflunomide, cyclosporine, sulphasalazine) on drug survival. Additional retention rate sub-analyses were performed for every disease on patients receiving golimumab as first line and second line of treatment.

Statistical analysis

Baseline characteristics were described as mean (standard deviation, SD) or median (interquartile range, IQR) values for continuous variables, according to normality of the distribution, and frequencies (percentages) for categorical variables.

Treatment persistence was assessed with Kaplan-Meier estimators. To compare crude survival between diagnoses and lines of treatment we used the log-rank test, while Cox proportional hazard models were used to adjust for confounders. *P*-values equal to or less than 0.05 were considered statistically significant.

Analyses were performed using SPSS v. 17.0 (SPSS, Chicago, IL, USA).

Results

Overall 410 subjects were included in the analysis: 180 patients with RA, 110 with PsA and 120 with AS. Baseline characteristics are reported in Table I. Patients with RA were older than subjects with PsA and AS, and showed a different distribution according to sex (females were more frequent among RA patients, and males in AS). More than 40% of the included subjects received golimumab as their first biological agent. Patients with RA were more likely to be treated with methotrexate or other sDMARDs (leflunomide, cyclosporine and sulphasalazine) than PsA and AS patients.

Table I. Baseline characteristics of the study population.

	Rheumatoid arthritis (n=180)	Psoriatic arthritis (n=110)	Ankylosing spondylitis (n=120)
Age, mean (SD)	54.6 (13.6)	47.9 (12.8)	45.2 (12.2)
Gender (female), n (%)	147 (81.7%)	55 (50%)	52 (43.3%)
Disease duration (years), median (IQR)	6.3 (3; 13.4)	6.6 (2.5; 11.3)	6.4 (1.9; 13.3)
Previous treatment with biological drugs, n (%):			
none	85 (47.2%)	47 (42.7%)	51 (42.5%)
one	51 (28.3%)	30 (27.3%)	42 (35%)
two or more	44 (24.5%)	33 (30%)	27 (22.5%)
Methotrexate, n (%)	123 (68.3%)	58 (52.7%)	27 (22.5%)
sDMARDs*, n (%)	145 (80.6%)	72 (65.5%)	38 (31.7%)
DAS28, mean (SD)	4.63 (1.33)	-	-
HAQ, median (IQR)	1 (0.5; 1.375)	-	-

*sDMARDs: synthetic disease-modifying anti-rheumatic drugs (including: methotrexate, leflunomide, sulphasalazine, cyclosporine).

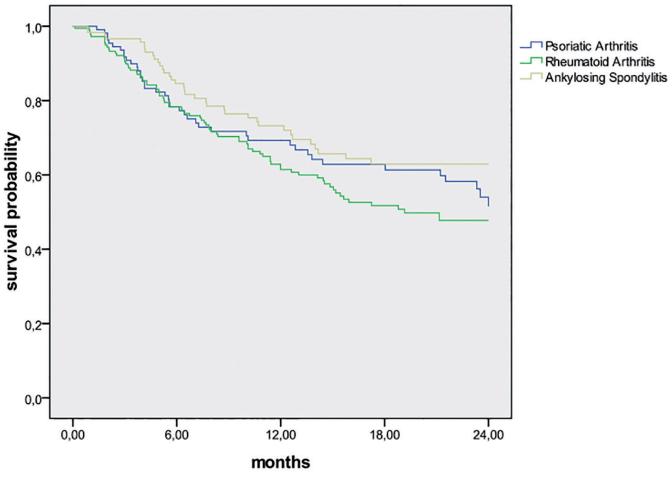

Fig. 1. Overall two-year retention rate of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

Two-year retention rates in the three diseases are depicted in Figure 1. The overall 2-year retention rate of patients with RA was 47.3%. Subjects with PsA showed a 2-year retention rate of 48%, and the 2-year retention rate of those with AS was 62.8%. Survival on treatment of patients with AS was significantly higher than that of RA patients (p=0.032) at the log-rank test, while no significant difference was found between AS and PsA and between RA and PsA (p=0.231 and p=0.380, respectively) (Fig. 1). However, after controlling for age, sex and disease duration, AS did not show a significantly better survival than RA (Table II). Male sex was associated with a lower discontinuation rate [HR (95% CI): 0.51 (0.35, 0.74)].

Among the 180 patients with RA, 80 subjects stopped the treatment with Golimumab due to inefficacy or adverse events before 24 months of treatment: 15 (8.3%) for adverse events and 65 (36.1%) for inefficacy. In PsA 42 events were observed [8 (6.2%) drug discontinuations for adverse events and 34 (30.9%) for inefficacy], while 36 subjects with AS stopped the treatment with golimumab: 9 (7.5%) for adverse events and 27 (22.5%) for inefficacy. No differences were observed among the three diseases in the cumulative incidence of discontinuation because of adverse events (RA *vs*. PsA: p=0.744; RA *vs*. AS: p=0.770; PsA *vs*. AS: p=0.991). Patients with AS showed a lower discontinuation rate due to inefficacy compared with RA (p=0.024), whereas no differences were found between AS and PsA (p=0.178) and between RA and PsA (p=0.415). Again, after controlling for age, sex and disease duration, AS did not show a significantly lower discontinuation rate than RA (Table II). Male sex was associated with a lower discontinuation

Table II. Cox proportional hazard ratios for treatment discontinuation among diseases.

	Overall		Adverse events		Inefficacy	
	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*
SA	ref	ref	ref	ref	ref	ref
APs	1.31 (0.84, 2.04)	1.29 (0.82, 2.01)	0.99 (0.38, 2.58)	0.97 (0.37, 2.55)	1.41 (0.85, 2.34)	1.39 (0.84, 2.31)
RA	1.53 (1.04, 2.28)	1.17 (0.77, 1.79)	1.14 (0.49, 2.59)	0.78 (0.31, 1.95)	1.67 (1.07, 2.61)	1.29 (0.80, 2.09)

*adjusted for age, sex, and disease duration.

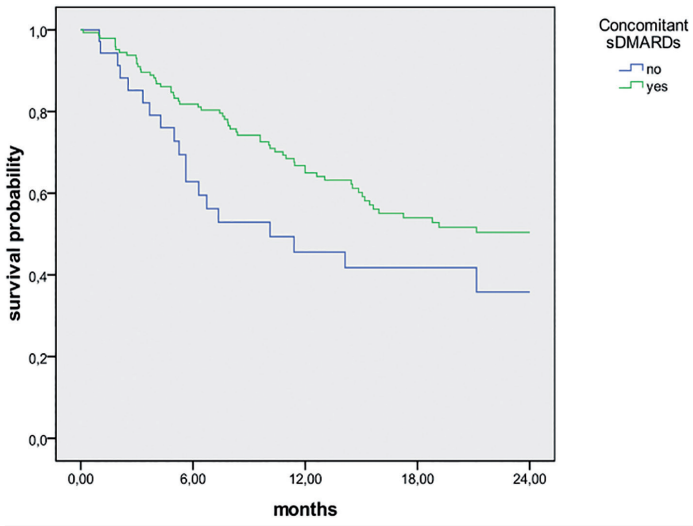

Fig. 2. Two-year retention rate of patients with rheumatoid arthritis treated with golimumab with and without concomitant sDMARDs.

rate for inefficacy [HR (95% CI): 0.48 (0.31, 0.73)].

When considering only patients with RA, Kaplan-Meier estimates showed a lower discontinuation rate for subjects treated with concomitant sDMARDs than for those receiving golimumab alone (2-year retention rate of 50% and 35.6%, respectively; p=0.046) (Fig. 2). This difference was still statistically significant after adjustment for age, sex and disease duration [HR (95%CI): 1.74 (1.04, 2.93)], and mainly related to a significant difference in treatment discontinuation for adverse events [HR (95%CI): 4.58 (1.62, 12.96)] than for inefficacy [HR (95%CI): 1.29 (0.69, 2.43)]. In subjects with RA, golimumab was given as first and second line treatment in 85 and 51 patients, with a 2-year retention rate of 49.1% and 53.4%, respectively; the comparison between first and second line of treatment groups did not show any significant difference in mean survival time (p=0.724) (Fig. 3A).

In patients with PsA, the 2-year discontinuation rate was not different between those receiving and not receiving a concomitant treatment with sDMARDs (p=0.85). When comparing patients who were treated with golimumab as first (n=47) and second (n=30) line of treatment, the 2-year retention rates were not significantly different (66.2% and 54%, respectively; p=0.333) (Fig. 3B).

Finally, among subjects with AS the concomitant treatment with sDMARDs did not significantly affect discontinuation rates (p=0.133). Golimumab was given as first and second line of treatment in 51 and 42 patients, and the comparison between the two groups did not show any significant difference in the 2-year retention rate (57.1% and 75.7%, respectively; p=0.127) (Fig. 3C).

Discussion

In this study we report on data about persistence on treatment with golimumab in RA, PsA and AS from an observational registry of Northern Italy. To our knowledge, no data have been published on this issue yet, so that it is the first report on real-life effectiveness of the treatment with golimumab assessed by retention rates. Retention rate is a reliable parameter to evaluate real-life effectiveness because it comprises different factors including efficacy, safety and patient's compliance to the treatment.

As expected, we found that patients with AS had a higher retention rate than subjects with RA, in line with the results of other observational studies on European and Italian registries (12-14). In our study, the higher retention rate in AS compared to RA may be ascribed to a lower discontinuation rate due to primary and secondary inefficacy, since the occurrence of discontinuation for adverse events was not significantly different in the three diseases. This observation may be explained by a better response to anti-TNF treatment in patients with a predominant axial involvement, but also by the absence of many other effective treatments in patients with AS, unlike RA and PsA (13). However, after adjustment for possible confounders such as age, sex and disease duration, the difference observed in our sample between AS and RA was no more significant. The results of this analysis suggest that factors related to patients' characteristics, such as a different distribution of sex among RA and AS patients, could have influenced the persistence on treatment more than factors related to the disease itself, so that golimumab could be expected to be similarly effective in RA, APs and AS.

In patients with RA, the use of concomitant sDMARDs (mainly methotrexate) was associated with a better survival on treatment. This observation is in line with other studies showing a higher retention rate in patients on anti-TNF therapy concomitantly treated with sDMARDs (15, 16). A higher efficacy of the treatment with golimumab in RA patients concomitantly treated with Methotrexate has emerged from RCTs (7). However, in our population the higher persistence on treatment was related to a lower discontinuation rate for adverse events, and not for ineffective-

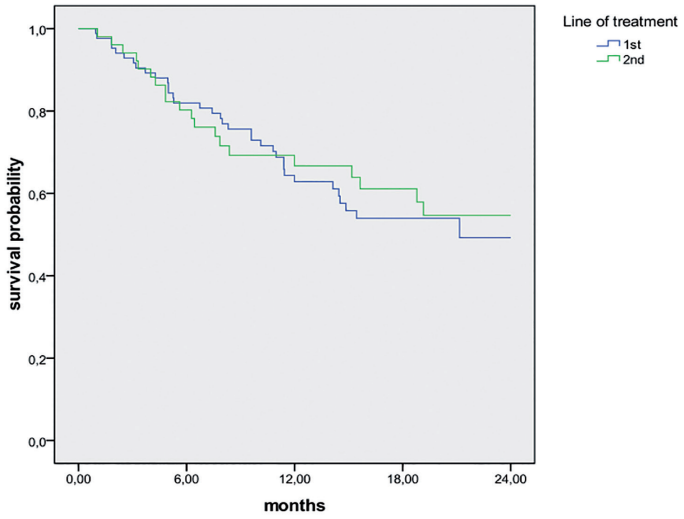

Fig. 3A. Two-year retention rate of patients with rheumatoid arthritis in first and second line of treatment.

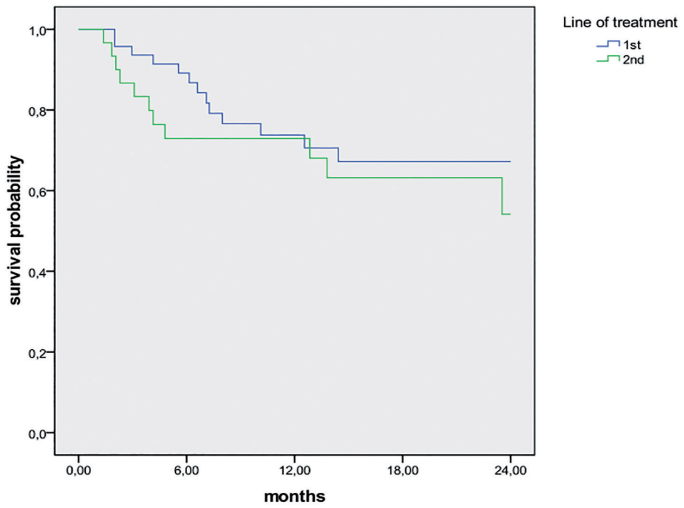

Fig. 3B. Two-year retention rate of patients with psoriatic arthritis in first and second line of treatment.

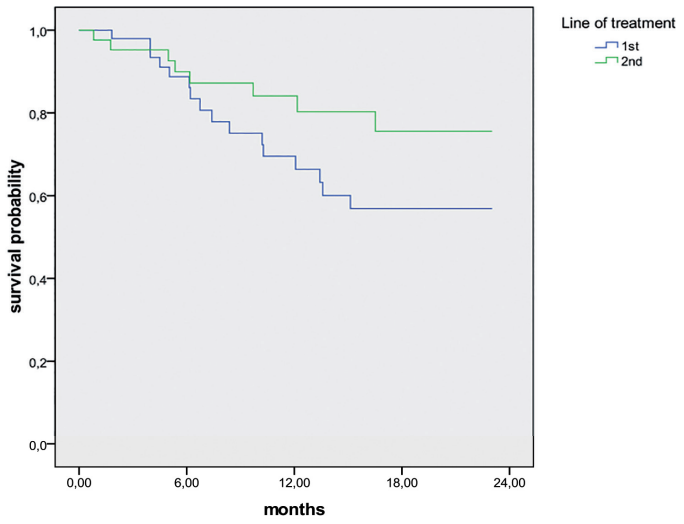

Fig. 3C. Two-year retention rate of patients with ankylosing spondylitis in first and second line of treatment.

ness. Even if other studies confirmed a lower incidence of adverse events in patients concomitantly treated with methotrexate (15), this observation should be considered with caution because it could be affected by a channelling bias, since patients at higher risk of adverse events are more likely to receive a less aggressive treatment.

Another interesting finding is the lack of a significant difference in retention rates between patients receiving golimumab as first biological treatment and those receiving the drug after a switch from a previous bDMARD. To date, golimumab is the only available anti-TNF whose efficacy has been demonstrated in a RCT specifically designed to evaluate the performance of a second TNF inhibitor in patients who failed a first one (the GO-AFTER study) (5). Our observation confirms in real life a good performance of golimumab as second line of treatment in RA, PsA and SA. However, even if some meta-analyses indirectly compared the clinical efficacy of golimumab emerging from RCTs to that of other TNF inhibitors (17), a direct comparison with other anti-TNF agents is not available yet, but it is expected to better clarify the comparative effectiveness of this drug in clinical settings.

Due to the observational and retrospective nature of our study, some limitations should be considered for our observations. First of all, due to the study design, no conclusions on treatment efficacy could be drawn on this data, but only observations on its real-life effectiveness. Moreover, we could adjust our analysis only for factors easily detectable in a clinical registry, but we could not exclude the influence on the results of other confounding variables. The definition of "inefficacy" that leads to treatment discontinuation depends on clinical evaluation and so it may be extremely variable among physicians. On the other hand, the main strength of our study is the high representativeness of the sample, including all the patients who were addressed to the treatment with golimumab in the tertiary rheumatology centres of Northern Italy that participate in the LORHEN registry.

In conclusion, to our knowledge this is the first report of real-life data on 2-year survival on treatment with golimumab in RA, PsA and AS. We observed a higher crude retention rate in patients with AS than in RA. The concomitant treatment with Methotrexate and other sDMARDs was associated with a better survival on treatment in patients with RA. A similar retention rate was found when golimumab was given as first and second-line of treatment.

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