Seminars in Arthritis and Rheumatism 47 (2017) 108–114

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Golimumab in real-life settings: 2 Years drug survival and predictors of clinical outcomes in rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis

Florenzo Iannone, MD, PhD[a,*,1], Leonardo Santo, MD[b,1], Maria Grazia Anelli, MD, PhD[a], Romano Bucci, MD[c], Angelo Semeraro, MD[d], Laura Quarta, MD[e], Francesca D'Onofrio, MD[f], Antonio Marsico, MD[d], Giorgio Carlino, MD[g], Oriana Casilli, MD[e], Fabio Cacciapaglia, MD, PhD[a], Carmelo Zuccaro, MD[h], Paola Chiara Falappone, MD[i], Francesco Paolo Cantatore, MD, PhD[f], Maurizio Muratore, MD[e], Giovanni Lapadula, MD[a]

[a] Rheumatology Unit, Department of Emergence Medicine and Transplantation (DETO), University of Bari, Piazza G Cesare, 11, 70124 Bari, Italy
[b] Unità Operativa di Reumatologia, ASL BT, Andria, Italy
[c] Rheumatology Hospital Unit, A.O.U. Foggia, Foggia, Italy
[d] Unità Operativa di Reumatologia, ASL Taranto, Taranto, Italy
[e] U.O. of Rheumatology, "V. Fazzi" Hospital, Lecce, Italy
[f] UOC Reumatologia Universitaria—University of Foggia, Foggia, Italy
[g] Rheumatology Service, ASL LE—DSS, Casarano and Gallipoli, Gallipoli, Italy
[h] Ambulatorio di Reumatologia Ospedale di Brindisi, Brindisi, Italy
[i] Internal Medicine Unit, S. Camillo de' Lellis Hospital, Mesagne, Italy

ARTICLE INFO

Keywords:
Drug survival
Golimumab
Predictors
Safety
Rheumatoid arthritis
Spondyloarthritis

ABSTRACT

Objectives: To assess the drug survival of golimumab, and predictors thereof, in patients affected with rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA) in a prospective observational cohort.
Methods: This is a non-interventional, longitudinal study on RA, SpA, and PsA patients starting treatment with golimumab. Endpoints were the 2 years persistence rate of golimumab and predictors of therapy discontinuation. Drug retention was analyzed using Kaplan–Meier and Cox models. Hazard ratios (HR) of golimumab discontinuation were estimated by Cox-regression hazard models.
Results: Of 416 patients starting golimumab, 171 biologic-naïve and 245 inadequate responders to prior biologic drugs, 88 had RA, 147 SpA, and 181 PsA. Global 2 years drug retention was 70.2%, with no different hazard of discontinuation among diseases or line of biologic treatment. The strongest predictor of golimumab discontinuation was female gender (HR = 1.95). Golimumab monotherapy was associated with higher risk drug interruption (HR = 1.67). Within SpA, predictors of golimumab discontinuation were female sex (HR = 4.19), and absence of extra-articular manifestations (HR = 4.60). In PsA, duration of disease was negatively associated to drug interruption (HR = 0.93), whereas golimumab monotherapy was positively (HR = 2.21) associated. Interestingly, failing to achieve a good EULAR response at 3 months was the only predictor of golimumab discontinuation for RA patients (HR = 3.03).
Conclusions: This study provided evidence that golimumab has high retention rate in real-life settings. SpA male patients with extra-articular manifestations, PsA patients on co-therapy with DMARDs, and RA patients attaining an early clinical response had the highest probability to continue golimumab over 2 years.

Introduction

Targeting tumor necrosis factor (TNF)-α is nowadays a milestone in the paradigm of treatment of rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA). Several randomized clinical trials (RCTs) have shown the efficacy of TNF-α inhibitors in halting the clinical evolution and anatomic damage progression of chronic polyarthritis in patients selected by strict inclusion criteria. However, patients in clinical practice may be quite different from RCTs [1] and therefore assessing the long-term effectiveness and safety of new drugs is becoming mandatory. A surrogate marker of effectiveness and safety of a treatment in

* Corresponding author.
E-mail address: florenzo.iannone@uniba.it (F. Iannone).
[1] Both the authors equally contributed to this work.

http://dx.doi.org/10.1016/j.semarthrit.2017.01.008
0049-0172/

real-world settings is the time of persistence on therapy. Several reports from registries, gathering clinical data from patients with RA on treatment with biological drugs across the world, have provided evidence that persistence rate of the first TNF-α inhibitors come on to the market, adalimumab, etanercept, and infliximab, was below 50% at 4–5 years [2,3]. Instead, PsA patients tend to have a slight higher survival rate of a first TNF-α blocker at 4 years [4], as well patients affected with SpA [5]. A few studies from a setting of standard of care have attempted to compare the outcomes of TNF-α inhibitors across different diseases, and findings from the Spanish registry of biologics, BIOBADASER, did show a significantly lower rate of drug persistence of adalimumab, etanercept, and infliximab in RA than in SpA patients [6]. Instead, to our knowledge, there is no study evaluating the outcome of a single TNF-α antagonist across different rheumatic diseases.

Golimumab, a more recent TNF-α blocker, is a humanized monoclonal antibody neutralizing soluble and cell membrane bound TNF-α that has been shown to be effective in RA [7], PsA [8], ankylosing spondylitis (AS) [9], and more recently in non-radiographic axial-SpA [10] by randomized clinical trials (RCTs). Golimumab efficacy and safety, and its capability to halt joint damage progression, have been further confirmed in the long-extension studies of RCTs [11–17]. Only a recent study has been focused on drug persistence of different TNF-α blockers in RA, PsA, and AS patients analyzing data from Swedish Prescribed Drug Register and showing a significantly higher drug survival of golimumab than adalimumab or etanercept at 3 years [18]. However, differences among diseases were not evaluated. In this study, we aimed at assessing the drug survival of golimumab in unselected patients with RA, PsA, and SpA in settings of real-life.

Patients and methods

Study design

GOAREL is a longitudinal, prospective, and observational study collecting clinical data from patients affected with RA, PsA, and SpA beginning treatment with golimumab at 9 rheumatologic centers in Apulia (South Italy). The participant units encompass hospital and community-based practices and cover all population of Apulia, roughly 4,000,000 people. The database started at June 2013 and for the purpose of this study data until December 2015 were analyzed. The study obtained the approval of the local ethics committees (Ethics Review Board of Policlinico of Bari, comitatoetico@policlinico.ba.it, protocol number 4827) and all patients have given their written informed consent to participate and to use their data for publication with explicit protection of identification. The study was conducted in compliance with Helsinki's declaration.

Patients

Biologic-naïve patients or inadequate responders (IR) to prior biological drugs prescribed golimumab were eligible for the study. Patients were consecutively enrolled and the decision to administrate golimumab was made by the rheumatologist on his own. All patients had active disease and fulfilled 2010 classification criteria for RA [19], or CASPAR criteria for PsA [20], or ASAS criteria for axial- (radiographic and non-radiographic) [21] or peripheral-SpA [22]. The choice of treatment was made by the rheumatologist on his own decision following good clinical practice guidelines, and golimumab was given at standard dosage, without loading dose, according to the market approval by regulatory authorities.

Clinical assessment

At baseline the following demographics and clinical characteristics were recorded: age, gender, weight and height measured by the treating physician, current smoking habit, rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) positivity, presence of HLA-B27 haplotype for axial SpA, number of tender and swollen joints, C-reactive protein (CRP, mg/l), erythrocyte sedimentation rate (ESR, mm/1st hour), duration of disease, concomitant therapy with glucocorticoids (prednisone equivalent) and conventional disease modifying anti-rheumatic drugs (cDMARDs), number of previous biological drugs, extra-articular manifestations (ocular, non-psoriasis skin involvement, and inflammatory bowel-disease). Comorbidities were coded by using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2) and according to the WHO classification of BMI categories, patients were classified into underweight/normal weight (BMI $\leq$ 25.0 kg/m^2), overweight (BMI $>$ 25.0 kg/m^2 $\leq$ 30 kg/m^2), and obese (BMI $>$30.0 kg/m^2). Patient reported outcomes (PROs) included functional disability by Health Assessment Questionnaire (DI-HAQ), duration of morning stiffness, assessment of pain and global disease activity, bath ankylosing spondylitis disease activity index (BASDAI). Clinical composite measures were ESR-disease activity Score on 28 joints (ESR-DAS28), clinical disease activity index (CDAI), ankylosing spondylitis disease activity score-CRP (ASDAS-CRP), and psoriasis area severity index (PASI). Clinical data and PROs were also collected at 3, 6, 12 months, and every year thereafter. Discontinuation of treatment and causes thereof were also recorded.

Statistical analysis

We analyzed patient demographics and disease characteristics at treatment initiation using standard descriptive statistics. Patients lost to follow-up or patients who stopped therapy due to reasons deemed unrelated to golimumab (pregnancy, relocation, clinical remission, or other) were right censored. Time to discontinuation was defined as the time between golimumab initiation and last administration plus 1 month (dispensation interval). Crude drug retention rate and mean survival time (MST) were estimated using Kaplan–Meier (K–M) life-table method and differences across SpA, PsA, and RA, gender (female/male) and line of biologic treatment (biologic-naïve/$\geq$1 biologic drug) were compared using the log-rank test. Drug-survival curves of SpA, PsA, and RA, were adjusted for patient demographics (age, gender, BMI, and smoking), disease characteristics (disease duration, HAQ-DI, and comorbidities), and treatment characteristics (number of prior biologic drugs, co-therapy with glucocorticoids, and cDMARDS). Estimated hazard ratios (HRs) of discontinuing golimumab at 2 years were assessed by performing a multivariate Cox regression with different models according to the disease group. Finally, 3-month achievement of good EULAR response (decrease in DAS28 $\geq$ 1.2 from baseline) was measured in RA and PsA patients. Missing data were about 5% and were not imputed.

Results

Patient demographics

We studied 416 patients starting a treatment with golimumab due to active SpA (n = 147) or PsA (n = 181) or RA (n = 88). In PsA cohort, 177 patients had peripheral joint involvement, and 35 had

Table 1
Baseline demographics of patients with spondyloarthritis (SpA), psoriatic arthritis (PsA), and rheumatoid arthritis (RA)

	All (n = 416)	SpA (n = 147)	PsA (n = 181)	RA (n = 88)
Age (mean ± SD)	52 ± 4	48 ± 11	53 ± 10	56 ± 13
Female, n (%)	274 (66)	75 (51)	128 (70)	71 (81)
BMI (kg/m^2) (mean ± SD)	26.8 ± 5	26.5 ± 4	27.5 ± 5	26.0 ± 5
Normal weight (BMI ≤ 25), n (%)	166 (40)	62 (42)	61 (34)	43 (49)
Overweight (BMI > 25 ≤ 30), n (%)	153 (37)	56 (38)	70 (38)	27 (31)
Obese (BMI > 30), n (%)	97 (23)	29 (20)	50 (28)	18 (20)
Duration disease (mean ± SD)	7.6 ± 7	7.4 ± 7	6.9 ± 6	8.1 ± 8
Current smokers, n (%)	74 (18)	25 (17)	36 (20)	13 (15)
Comorbidities, n (%)	263 (63)	74 (50)	130 (72)	59 (67)
Extra-articular manifestations, n (%)	119 (29)	38 (26)	24 (13)	9 (10)
ESR, mm/1st hour	23 ± 17	21 ± 16	22 ± 17	28 ± 19
CRP, mg/l	8.1 ± 14	7.4 ± 8.8	6.2 ± 12	13 ± 24
ESR-DAS28 (mean ± SD)	4.4 ± 1.2	4.1 ± 1.2	4.3 ± 1.1	5.0 ± 1.4
CDAI	20.2 ± 11	17.6 ± 8.9	18.6 ± 10	26.1 ± 12
PASI	–	–	1.5 ± 2.7	–
BASDAI (mean ± SD)	6.0 ± 2	6.1 ± 1	5.9 ± 2	–
HAQ-DI (mean ± SD)	1.4 ± 0.8	1.5 ± 1.1	1.3 ± 0.7	1.7 ± 0.7
RF/ACPA, n (%)	–	–	–	58 (73)
1st line biologic, n (%)	171 (41)	56 (38)	74 (41)	41 (47)
≥2nd line biologic, n (%)	245 (59)	81 (62)	107 (59)	47 (53)
Glucocorticoids, n (%)	249 (60)	63 (43)	105 (58)	81 (92)
Combination with cDMARDs, n (%)	316 (76)	86 (58)	105 (58)	80 (91)

Values are the mean 1 SD unless otherwise indicated. BMI = body mass index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = 28 joints disease activity score; CDAI = clinical disease activity index; BASDAI = bath ankylosing spondylitis disease activity index; HAQ-DI = health assessment questionnaire-disability index; RF/ACPA = rheumatoid factor/anti-citrullinated peptide antibody; cDMARDs = conventional disease modifying anti-rheumatic drugs.

associated axial disease, and 4 patients had psoriatic spondylitis. Among SpA patients, 100 had radiographic or non-radiographic axial-SpA and 47 peripheral SpA. Comprehensive demographics and baseline clinical data of the whole cohort and of the single disease group are shown in Table 1.

Global drug survival

Crude drug survival was estimated by K–M curves and the global retention rate was 70.2% at 2 years, being MST = 19.9 (95% CI: 19.1–20.6) months. Comparing the drug survival among disease groups, retention rate was higher for SpA [78.2%, MST = 21.3 (95% CI: 20.2–22.3) months] than RA [63.6%, MST = 19.3 (95% CI: 17.7–21.0) months] or PsA [66.9%, MST = 19.0 (95% CI: 17.8–20.2) months] (log rank, p = 0.04) (Fig. 1A). However, adjusting survival curves for baseline factors by Cox-regression proportional hazard model (Fig. 1B), HRs of discontinuing golimumab at 2 years were not significantly different among SpA, PsA, and RA. Only gender was strongly associated to drug discontinuation, having females double the hazard to interrupt golimumab as compared to males (HR = 1.9, 95% CI: 1.18–3.23) (Table 2). Furthermore, patients who prescribed golimumab without concomitant cDMARDs had increased hazard to stop the therapy (HR = 1.6, 95% CI: 1.05–2.66). Interestingly, neither BMI status nor the line of biological treatment were significantly correlated to 2 years drug survival (Table 2).

We then explored the impact of gender and line of biological treatment on drug retention of golimumab at 2 years for each disease by K–M analysis. Globally, male patients (Fig. 1C) showed a significantly higher drug retention rate [83.1%, MST = 21.8 (95% CI: 20.8–22.8) months] than females [63.5%, MST = 18.9 (95% CI: 18.0–19.9) months] (log rank, p = 0.0001). Considering each disease, male PsA patients had a higher drug retention rate [73.6%, MST = 20.5 (95% CI: 18.5–22.5) months] than females [64.1%, MST = 18.4 (95% CI: 17.0–19.8) months], but the difference was not statistically significant (Fig. 1D). In RA patients, males [76.5%, MST = 20.4 (95% CI: 16.1–24.6) months] and females [60.6%, MST = 19.1 (95% CI: 17.2–21.0) months] had similar drug survival curves (Fig. 1E). In SpA, a highly significant difference between genders was detected (Fig. 1F), as drug-survival rate was much higher in males [91.7%, MST = 23.0 (95% CI: 22.0–24.0) months] than in females [65.3%, MST = 19.6 (95% CI: 17.8–21.4) months].

A further interesting finding was drug survival of golimumab in IR-biologic patients. Considering the whole cohort of patients on golimumab, 2 years K–M persistence rates in naïve-biologic [67.3%, MST = 19.4 (95% CI: 18.3–20.6) months] and IR-biologic [72.2%, MST = 20.2 (95% CI: 19.2–21.5) months] patients were very similar. While in PsA and in SpA patients drug survival among the different lines of treatment with golimumab were similar (data not shown), drug survival in RA was higher in naïve-biologic [75.6%, MST = 20.9 (95% CI: 18.8–23.1) months] than in IR-biologic [53.2%, MST = 18.0 (95% CI: 15.5–20.5) months] patients, but the difference did not reach the statistical significance (log rank, p = 0.06).

Table 2
Estimated hazard ratios (HR) of 2 years drug discontinuation for all patients treated with golimumab by Cox-regression proportional hazard analysis

Covariates	Beta	p Value	HR	95% CI	
Spondyloarthritis			1		
Psoriatic arthritis	0.286	0.242	1.332	0.824	2.151
Rheumatoid arthritis	0.101	0.723	1.106	0.633	1.934
Female/male	0.671	0.009	1.956	1.182	3.236
Obese			1.00		
Normal weight	0.597	0.247	1.816	0.661	4.990
Overweight	0.451	0.222	1.570	0.761	3.242
BMI (kg/m^2)	0.048	0.212	1.049	0.973	1.131
Age	−0.003	0.705	0.997	0.980	1.014
Duration of disease	−0.005	0.749	0.995	0.967	1.024
Smoking (no/yes)	0.053	0.859	1.054	0.588	1.889
cDMARDs (no/yes)	0.515	0.030	1.673	1.050	2.668
Glucocorticoids (no/yes)	−0.308	0.158	0.735	0.479	1.127
Comorbidities (no/yes)	−0.108	0.625	0.897	0.581	1.387
Biologic naïve (yes/no)	0.209	0.305	1.233	0.827	1.839
HAQ-DI	0.176	0.099	1.192	0.968	1.469

BMI = body mass index; cDMARDs = conventional disease modifying anti-rheumatic drugs; HAQ-DI = health assessment questionnaire-disability index; CI = confidence intervals.

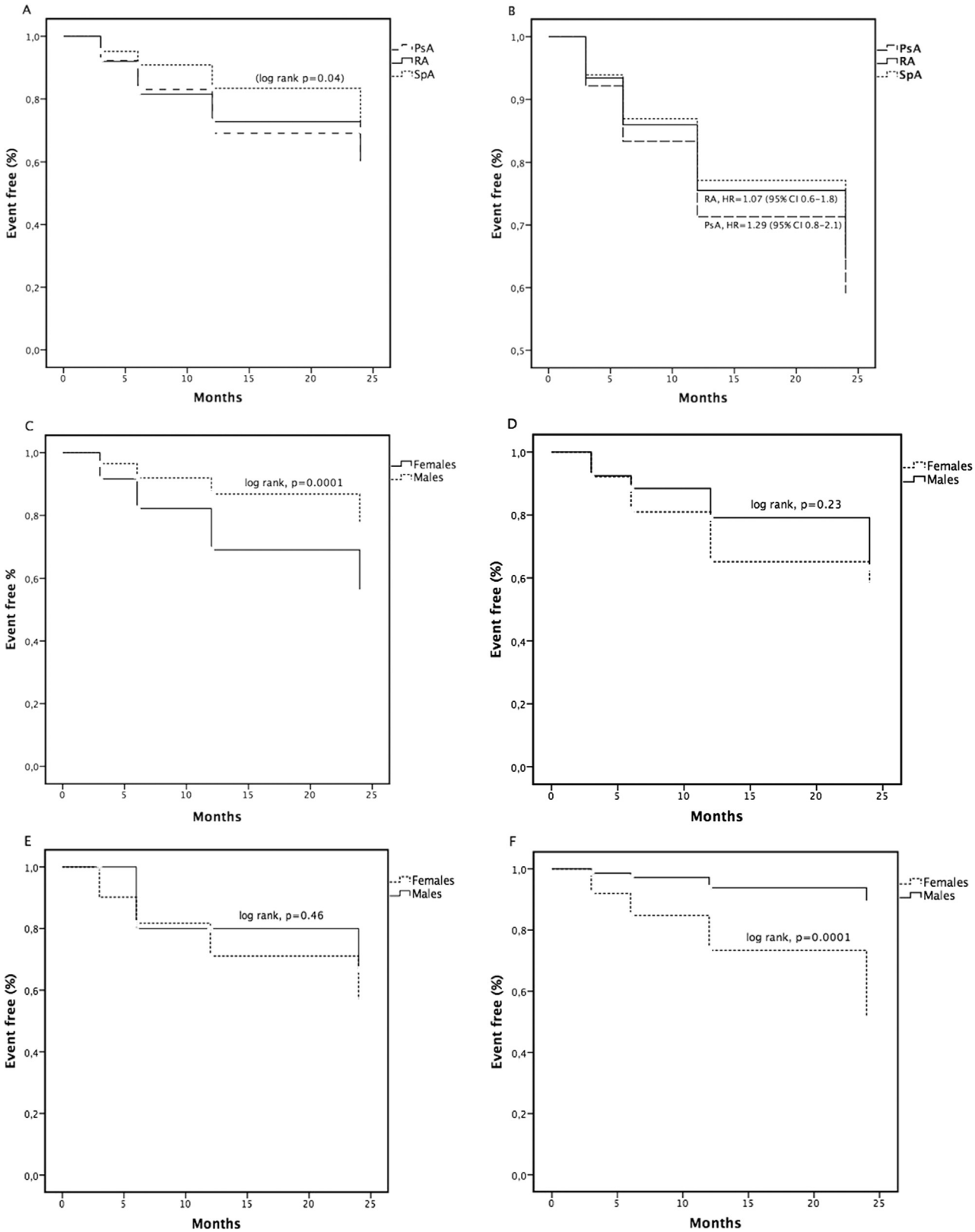

Fig. 1. Two-year survival curve analysis of golimumab. (A) Drug survival assessed by Kaplan–Meier life-table method and comparison among spondyloarthritis (SpA), psoriatic arthritis (PsA), and rheumatoid arthritis (RA). (B) Drug-survival curves after adjustment for baseline factors (Table 2) by Cox-regression proportional hazard model. HR, hazard ratio; CI, confidence interval, SpA = Ref. [1]. (C) Kaplan–Meier survival curves by gender in the whole cohort. (D) Kaplan–Meier survival curves by gender in PsA patients. (E) Kaplan–Meier survival curves by gender in RA patients. (F) Kaplan–Meier survival curves by gender in SpA patients.

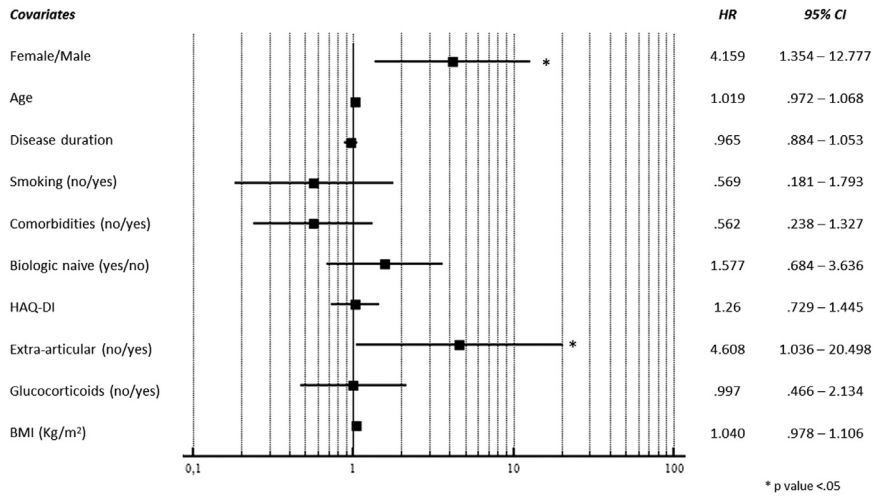

Fig. 2. Forest plot of hazard ratio (HR) of discontinuing golimumab adjusted for baseline factors in spondyloarthritis patients. HAQ-DI, health assessment questionnaire-disability index; BMI, body mass index.

Predictors of drug survival by disease

Multiple Cox-regression analysis was used to search for possible predictors of 2 years golimumab discontinuation in each disease cohort. In SpA group (Fig. 2), patients with higher hazard to stop the therapy were females (HR = 4.1, 95% CI: 1.35–12.77), and those without extra-articular manifestations (HR = 4.6, 95% CI: 1.03–20.49). In RA patients (Fig. 3), no baseline factors, such as gender, BMI, HAQ, and co-therapy with cDMARDs, were correlated with drug discontinuation, while the strongest predictor of golimumab interruption was failing to achieve a good EULAR response at 3 months (HR = 3.0, 95% CI: 1.26–7.30). Finally, in PsA cohort (Fig. 4), duration of disease was negatively associated with golimumab discontinuation (HR = 0.9, 95% CI: 0.95–1.00), and golimumab monotherapy without combination with cDMARDs was positively correlated to drug interruption (HR = 2.2, 95% CI: 1.13–4.30).

Safety

Golimumab was safe and well tolerated. Of 124 (29.8%) patients stopping treatment with golimumab, 80 (19.2%) withdrew due to ineffectiveness, 20 (4.8%) due to adverse events, and 24 (5.8%) due to other causes. Adverse events causing interruption of therapy were 5 gastrointestinal, 2 shingles, 3 pulmonary, 3 neoplasia (1 breast cancer, 1 ovarian cancer, and 1 menigioma), 2 hematological (1 neutropenia and 1 thrombocytopenia), 1 peripheral neuropathy, 1 cerebral vasculopathy, 1 dental abscess, 1 skin rash, and 1 flare of skin psoriasis.

Discussion

The knowledge of long-term effectiveness and safety of biologic drugs in real world outside the settings of RCTs is becoming always more demanding, and little is known about golimumab. Here, we presented the 2 years drug survival of golimumab in a prospective cohort of patients with RA, SpA, and PsA beginning the therapy in settings of standard of care, showing that RA and PsA patients had a comparable hazard to discontinue the treatment of SpA patients. Previously, a retrospective analysis from BIOBADASER register [6] had showed that anti-TNFα drugs, adalimumab, etanercept, and infliximab, as first biological treatment, had higher 3-year survival rate in SpA than in RA, maybe due in part to a lower incidence of adverse events in SpA. No sub-analysis within each anti-TNF-α drug was estimated. In SpA group were included patients with AS, PsA, undifferentiated SpA, Crohn associated SpA, and juvenile SpA.

According to Assessment of SpondyloArthritis International Society (ASAS) criteria [21, 22], we distinguished SpA in axial- and peripheral-SpA by keeping apart PsA, and evaluated the drug

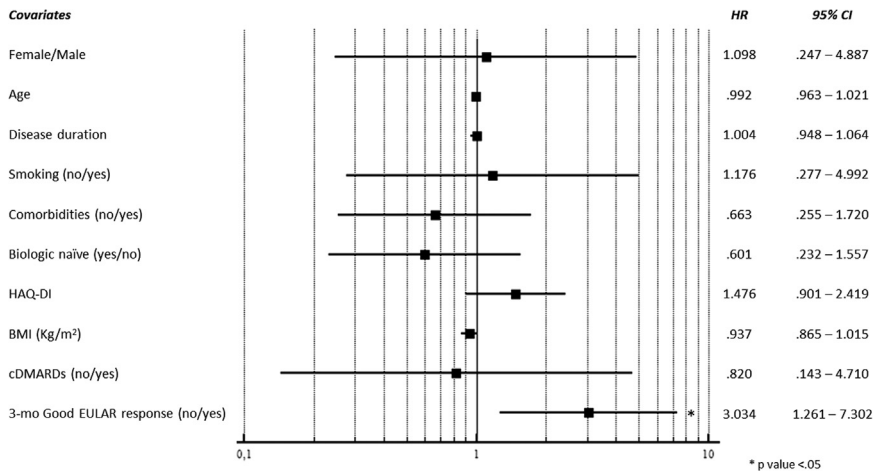

Fig. 3. Forest plot of hazard ratio (HR) of discontinuing golimumab adjusted for baseline factors and 3-month good EULAR response in rheumatoid arthritis patients. HAQ-DI; health assessment questionnaire-disability index, BMI, body mass index, cDMARDs; conventional disease modifying drugs.

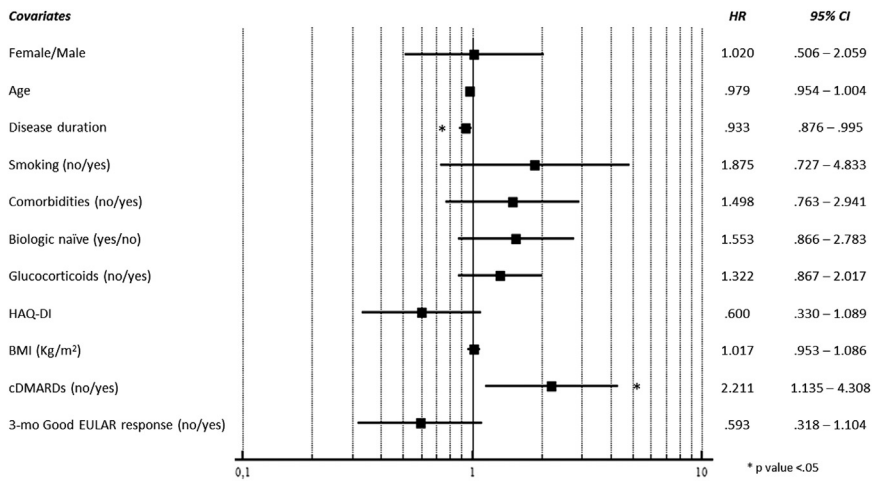

Fig. 4. Forest plot of hazard ratio (HR) of discontinuing golimumab adjusted for baseline factors and 3-month good EULAR response in Psoriatic Arthritis patients. HAQ-DI, health assessment questionnaire- disability index; BMI, body mass index; cDMARDs, conventional disease modifying drugs.

survival of golimumab in each disease and estimated the association of treatment discontinuation with baseline demographics and disease characteristics. Crude survival analysis by K–M curves showed a significant higher rate of drug retention in SpA than in RA or PsA. Of note, in our cohort the 2 years retention rate of golimumab in SpA patients was 78%, while the percentage of biological-naïve AS patients still on treatment with golimumab reported in the RCT GO-RAISE at 104 weeks was to 81% [12]. However, when survival analysis was adjusted by demographics and disease characteristics, the chance to continue golimumab was similar across diseases.

Instead, we found peculiar factors that were associated to drug discontinuation within each disease. In SpA the strongest predictor of golimumab discontinuation were female gender and lack of extra-articular manifestations. The benefit of combining anti-TNF-α drugs with cDMARDs in PsA patients is matter of debate and the long-extension study of GO-REVEAL has showed that the co-therapy was not more favorable than monotherapy to achieve the state of minimal disease activity at 5 years, but enabled a significant decrease in radiographic damage progression [23]. Consistently, in our study PsA patients taking golimumab as monotherapy had double the hazard of discontinuing the treatment.

In RA patients no baseline factor was correlated with drug interruption, including HAQ and BMI. The latter has been reported to be a negative predictor of drug survival of adalimumab, infliximab, and etanercept in RA patients [24]. Further analysis on larger cohorts are needed to assess the impact of high BMI on clinical outcomes of golimumab in RA patients. Apart from some general characteristics, there is no current baseline tool letting the physicians envisage the clinical response before starting a treatment in an individual patient, therefore, capturing as soon as possible an early clinical outcome capable of predicting the late response could aid in the decision-making strategy, whether continuing or stopping the therapy. In RCTs, it has been shown that clinical response within the first 3 months is related to the level of disease activity at 1 year in RA patients taking adalimumab, infliximab, etanercept, regardless of the disease duration [25]. In clinical practice, the achievement of a good EULAR response at 3 months was a strong predictor of a state of low disease activity at 12 months in RA patients on treatment with certolizumab [26]. In this study, the 3-month good EULAR response was strictly associated to drug survival in RA, and patients failing to early achievement of a good EULAR response had 3-fold higher the hazard to discontinue golimumab within 2 years.

Unlike RCTs, in our cohort unselected patients irrespective of the prior treatment were enrolled. Biologic-naïve patients were 41% and the remaining were biologic-IR patients with up-to sixth line of treatment. In the GO-AFTER trial, golimumab was effective in RA patients with active disease who had previously received one or more TNF-α inhibitors, regardless the cause of discontinuation and number of prior anti-TNF-α drugs [27]. In our study, we did not found a significant difference between biologic-naïve and biologic-IR patients in terms of drug survival, and, even after adjustment for possible confounding factors, biologic-IR patients did not have higher hazard to discontinue golimumab. Similar findings have been reported by a retrospective analysis in a Japanese study on a small cohort of RA patients [28].

Despite of the usual flaws of the observational studies, such as lack of a control group, no assessment of structural damage, or possible missing of minor adverse events, this was a prospective study focused on effectiveness and safety of golimumab across the approved indications, RA, SpA, and PsA, in real-world settings. No disease specific hazard of golimumab discontinuation arose, and 2 years drug survival was tightly associated to male gender and presence of extra-articular manifestations in SpA, combination therapy with cDMARDs in PsA, and early achievement of good EULAR response in RA.

Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Iannone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Iannone, Santo, and Lapadula

Acquisition of data: Santo, Anelli, Bucci, Semeraro, Quarta, D'Onofrio, Marsico, Carlino, Casilli, Cacciapaglia, Zuccaro, Falappone, Cantatore, Muratore, and Lapadula.

Analysis of data: Iannone and Santo

Interpretation of data: All the authors.

References

[1] Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum 2006;54:3399–407.

[2] Iannone F, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, et al. Longterm retention of tumor necrosis factor-α inhibitor therapy in a large Italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. J Rheumatol 2012;39:1179–84.
[3] Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2015;74:354–60.
[4] Iannone F, Lopriore S, Bucci R, Lopalco G, Chialà A, Cantarini L, Lapadula G. Longterm clinical outcomes in 420 patients with psoriatic arthritis taking anti-tumor necrosis factor drugs in real-world settings. J Rheumatol 2016;43:911–7.
[5] Lie E, Kristensen LE, Forsblad-d'Elia H, Zverkova-Sandström T, Askling J, Jacobsson LT, et al. The effect of comedication with conventional synthetic disease modifying antirheumatic drugs on TNF inhibitor drug survival in patients with ankylosing spondylitis and undifferentiated spondyloarthritis: results from a nationwide prospective study. Ann Rheum Dis 2015;74:970-8.
[6] Carmona L, Gómez-Reino JJ, BIOBADASER Group. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. Arthritis Res Ther 2006;8:R72.
[7] Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68:789–96.
[8] Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60:976–86.
[9] Inman RD, Davis JC, Heijde Dv, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58:3402–12.
[10] Sieper J, van der Heijde D, Dougados M, Maksymowych WP, Scott BB, Boice JA, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2015;67:2702–12.
[11] Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis 2010;69:1129–35.
[12] Braun J, Deodhar A, Inman RD, van der Heijde D, Mack M, Xu S, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. Ann Rheum Dis 2012;71:661–7.
[13] Kavanaugh A, McInnes IB, Mease PJ, Krueger GG, Gladman DD, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. Ann Rheum Dis 2013;72:1777–85.
[14] Keystone EC, Genovese MC, Hall S, Miranda PC, Bae SC, Palmer W, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-FORWARD study extension. J Rheumatol 2013;40:1097–103.
[15] Kavanaugh A, McInnes IB, Mease P, Krueger GG, Gladman D, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Ann Rheum Dis 2014;73:1689–94.
[16] Deodhar A, Braun J, Inman RD, van der Heijde D, Zhou Y, Xu S, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. Ann Rheum Dis 2015;74:757–61.
[17] Keystone EC, Genovese MC, Hall S, Bae SC, Han C, Gathany TA, et al. Safety and efficacy of subcutaneous golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: final 5-year results of the GO-FORWARD trial. J Rheumatol 2016;43:298–306.
[18] Dalén J, Svedbom A, Black CM, Lyu R, Ding Q, Sajjan S, et al. Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence. Rheumatol Int 2016;36:1–9.
[19] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.
[20] Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
[21] Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.
[22] Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25–31.
[23] Kavanaugh A, van der Heijde D, Beutler A, Gladman D, Mease P, Krueger GG, et al. Radiographic progression of patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy: results through 5 years of a randomized, placebo-controlled study. Arthritis Care Res (Hoboken) 2016;68:267–74.
[24] Iannone F, Lopalco G, Rigante D, Orlando I, Cantarini L, Lapadula G. Impact of obesity on the clinical outcome of rheumatologic patients in biotherapy. Autoimmun Rev 2016;15:447–50.
[25] Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226–35.
[26] Iannone F, Carlino G, Marchesoni A, Sarzi-Puttini P, Gorla R, Lapadula G, et al. Early clinical response predicts low disease activity at one year in rheumatoid arthritis patients on treatment with certolizumab in real-life settings. An appraisal of the Italian registry GISEA. Joint Bone Spine 2016;83:721–5.
[27] Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374:210–21.
[28] Shono E. Effectiveness of golimumab in clinical management of patients with rheumatoid arthritis. Drugs R D 2013;13:95–100.