High 3-year golimumab survival in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: real world data from 328 patients

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Abstract

Objective

Our primary objective was to study the long-term survival on drug (SOD) of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) treated with golimumab (GLM) in real life settings.

Methods

This was a retrospective, observational study of all patients treated with GLM in 4 Academic Centres in Greece during a 4-year period (09/2010–06/2014). SOD was analysed using Kaplan-Meier survival analysis, while Cox regression analysis estimating hazard ratios (HRs) for different baseline variables associated with drug discontinuation was performed for each disease.

Results

328 patients (RA: 166, PsA: 82, AS: 80) were included. The estimated SOD at 2 and 3 years was 68% and 62% overall and was better for AS (79% and 76%) compared to RA (69% and 60%, p=0.067) and PsA (58% and 53%, p=0.001) patients; no difference was noted between RA and PsA patients (p=0.204). There was no difference in SOD between biologic-naïve and experienced nor between non-biologic co-treated or GLM monotherapy treated patients. Seropositivity (rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies) was associated with a lower risk for GLM discontinuation by multivariate analysis (HR=0.5, 95% CI=0.0.25–1.1, p=0.05) in RA patients. During 606 patient-years of follow-up, 11 (3.3%) patients discontinued GLM due to adverse events (AE), accounting for 11% of treatment discontinuations. The rates of serious AEs and serious infections were 2.3 and 1.0/100-patient-years, respectively.

Conclusion

In this real-life study, GLM showed a high 3-year SOD in patients with inflammatory arthritides with a low rate of discontinuation due to AEs.

Key words

golimumab, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

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Introduction

The introduction of biologic therapies revolutionised clinical practice in rheumatology over the last 15 years. Tumour necrosis factor (TNF) inhibitors was the first class of biologic disease modifying anti-rheumatic drugs (bDMARDs) which were licensed for the treatment of various rheumatic diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Their introduction in daily clinical practice was based on well-designed, randomised controlled trials (RCTs) in patients who were naïve or resistant to conventional synthetic DMARDs (csDMARDs) as well as in patients who had failed anti-TNFs (anti-TNF experienced) (1).

Although RCTs and their long-term trial extension studies (TES) (2-4) provide the strongest evidence for the efficacy and safety of anti-TNFs, they have certain inherent limitations such as the exclusion of patients with co-morbidities, their short-term duration and their drug discontinuation in patients who experience common adverse events (AEs, *i.e.* serious infections). Thus, as the number of rheumatic patients who are being treated with these agents increases worldwide, there is a clinical need for long-term, real life data concerning their safety and efficacy in daily clinical practice. Such real world evidence (RWE) data have been derived from patient registries (5), long term observational cohorts and administrative health databases (6). Most RWE data so far are available for infliximab, etanercept and adalimumab (5) and less so for golimumab (GLM) (7-10).

In this retrospective, observational study, we assessed the long-term clinical efficacy of GLM in a large cohort of patients with different inflammatory arthritides (RA, PsA, AS) by estimating the survival on drug (SOD), reasons of discontinuations and predictors thereof and its effect on disease activity parameters.

Materials and methods

Patients

We conducted a multicentre, retrospective, longitudinal, observational study including patients with RA, PsA or AS ever treated with at least one dose of GLM during a 4-year period (September 2010–June 2014). Patients were identified and followed from four Academic Rheumatology Centres in Greece (Joint Rheumatology Program, 1st Propedeutic Department of Medicine and 2nd Department of Medicine, National and Kapodistrian University of Athens, Division of Rheumatology, Clinical Immunology and Allergy of the Medical School of the University of Crete and Rheumatology Clinic, University of Ioannina). The data were extracted from the patients' files in a common database by the Division of Rheumatology, Clinical Immunology and Allergy of the University of Crete.

Inclusion criteria were age ≥18 years and one of the following: diagnosis of RA based on the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria, PsA based on the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria and AS based on the Assessment of SpondyloArthritis International Society (ASAS) criteria. Data were anonymously collected via a standardised procedure. Demographics (age, gender) and disease characteristics (disease duration, seropositivity for RA patients), disease activity for peripheral arthritis (*i.e.* swollen-SJC and tender joint count-TJC, Disease Activity Score 28-DAS28-ESR, DAS28-CRP, Clinical Disease Activity Index-CDAI, Simple Disease Activity Index-SDAI, Patient's Global Assessment) and for axial skeletal involvement (Bath Ankylosing Spondylitis Disease Activity Index-BASDAI), as well as indices of function (Health assessment questionnaire disability index-HAQ-DI and Bath Ankylosing Spondylitis Functional Index - BASFI) were recorded at the time of GLM initiation. Disease activity was recorded at 3–6 months intervals. For each participant, the number and type of csDMARDs and bDMARDs prescribed before GLM initiation were recorded and co-administration of csDMARDs and corticosteroids during GLM treatment was also documented. All patients were treated with the recommended dose for GLM (50 mg subcutaneously every month).

Reasons for GLM discontinuation were

classified as failure (primary or secondary), adverse events or other. AEs during GLM administration were recorded with the use of a separate form including the date and cause of the event and the need for hospitalisation.

All patients included in the patient registries of the participating centres were giving an informed consent upon first registration. An ethical approval for extraction and analysis of data in a blinded fashion was provided by the local institutional boards of participating centres.

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Statistical analysis

All statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, v. 20.0. Armonk, NY: IBM Corp). Demographic and descriptive data were expressed as medians (IQR). Chi square or Fisher's exact test was used for comparison of dichotomous and Mann-Whitney or *t*-test for continuous variables. GLM SOD was evaluated with Kaplan-Meier analysis and log rank test was implemented to compare SOD among the different groups. Patients were censored at GLM discontinuation for any reason (failure, adverse event, other) or at the end of follow-up. Those patients that were lost to follow-up, were considered to continue GLM until the last available visit, when they were censored.

Univariate and multivariate Cox regression analysis was used in order to identify baseline factors associated with GLM discontinuation. According to disease, several variables were tested in univariate Cox regression analyses and those with p-value <0.25 were included in the multivariate model. Variables with p-value <0.1, as well as those of biological significance (sex and age), were retained until the final stage of multivariate analysis (backward selection).

Regarding adverse events, time from GLM initiation to event, total incidence and the incidence of hospitalisations, infections and severe infections per 100 patient-years were calculated.

Results

Baseline patient characteristics

328 patients were included in the study: 166 with RA and 162 with spondyloarthropathies (SpA) (PsA: n=82, AS: n=80). The baseline patients' characteristics are shown in Table I. The mean age of patients was higher in RA patients (58.3±13.3 years) compared to PsA (52.1±11.9 years) and AS (45.7±11.3 years) patients (p<0.001 for both). As expected, patients with RA were more commonly women (89.2%) compared to PsA (67%) and AS (51%) patients (p<0.001 for both). Across patient subgroups, most of the patients had established disease; the median disease duration ranged from 6.9 years in RA patients to 9.7 years in AS patients.

Disease activity at baseline, as assessed by the DAS28 score was high in both RA (5.45±0.92) and PsA (5.24±1.3) patients. Similarly, AS patients had highly active axial disease assessed by the BASDAI (6.1±1.3) and impaired function assessed by BASFI (6.2±1.9).

The majority of patients had been previously exposed to ≥1 bDMARDs (RA: 54.8%, PsA: 59.7%, AS: 70%) prior to GLM initiation. GLM was administered as combination with csDMARD in 87% of both RA and PsA patients (most often MTX, 77.7% of RA) and in 54% of patients with AS. CS were used more commonly in RA patients (49%) and less so in SpA (10-18%) patients.

Treatment response

Almost half of the RA patients (45.2%) were naïve to biologic therapies and had highly active disease and impaired function (HAQ-DI, 0.96±0.39) at GLM initiation, despite use of background therapies. The clinical response was assessed by changes in the DAS28(ESR) (Fig. 1A). A gradual decrease in DAS28(ESR) from baseline (5.45±0.92) was depicted at 6 (4.25±1.12), at 12 (3.75±0.95), 24 (3.03±0.96) and 36 (2.96±1.19) months respectively (p<0.001 for all comparisons compared to baseline). The DAS28 remission rate (<2.6) at the respective time points were 7%, 11%, 26% and 46%, while low disease activity rate (<3.2) was achieved in 14%, 22%, 63% and 70% of patients still on the drug. Similar were the results for remission according to CDAI and SDAI scores (shown in Supplementary Table I).

The PsA cohort included 82 patients with rather established disease (median disease duration: 9 years) (Table I). The median DAS28(ESR) and HAQ-DI at baseline were 5.24±1.3 and 0.87±0.46, respectively. As found in RA-treated patients, a gradual improvement in disease activity was shown in PsA patients (Fig. 1B). The DAS28(ESR) decreased from 5.24±1.3 at baseline to 3.85±1.3 at 6, 3.52±1.57 at 12, 2.60±0.87 at 24 and 2.4±1.13 at 36 months (p<0.01 for all time points compared to baseline). No detailed data were available for analysis regarding changes in skin psoriasis during therapy.

Patients with AS had mostly established disease (n=80, median duration: 9.7 years), 30% were bDMARD-naïve while GLM was administered as monotherapy in 46% (Table I). Data on BASDAI and BASFI were available in 62 (77.5%) and 32 (40%) of patients at baseline and their mean values were 6.1±1.3 and 6.2±1.9 respectively. In AS patients, GLM induced a significant decrease of BASDAI from 6.1±1.3 at baseline to 3.77±1.73 at 6, 3.07±2.44 at 12, 1.77±2.83 at 24 and 2.5 ±2.59 at 36 months, respectively (p<0.05 for all time points compared to baseline).

Overall survival on drug

At the end of the follow-up, the total cohort has been followed for a mean time of 22.3±15.3 months (median: 18.3 months, Table I). In total, 200 out of the 328 patients (61%) were still on GLM, 30% (n=99) had stopped treatment while 9% (n=29) were lost to follow-up. Among treatment discontinuations most were due to drug inefficacy (n=81, 82%) and less so for AEs (n=11, 11%) or other reasons (n=7, 7%). There were no differences in the causes of drug discontinuation between the three patient subgroups (p=0.246).

The SOD expressed as the mean time on GLM tended to be higher for AS (43.4±2.2 months) compared to RA

Table I. Baseline patient characteristics according to diagnosis. Numbers are presented as mean values ±1 SD (median), unless otherwise indicated.

	Patient characteristics		
	RA (n=166)	PsA (n=82)	AS (n=80)
Demographics			
Age, years	58.3 ± 13.3	52.1 ± 11.9	45.7 ± 11.3
Sex, women, n (%)	148 (89.2)	55 (67)	41 (51)
Disease duration, years	9.9 ± 8.7 (6.9)	9.3 ± 6.6 (9)	10.4 ± 7.6 (9.7)
Seropositive (RF or anti-CCP)	42%	NA	NA
Disease activity			
DAS28 (ESR)	5.45 ± 0.92 (5.42), n=158	5.24 ± 1.3 (5.37) n=76	4.1 ± 1.2 (3.8) n=42
DAS28 (CRP)	4.3 ± 0.83 (4.4) n=144	4.0 ± 1.2 (4) n=71	3.1 ± 1.1 (4) n=35
BASDAI	NA	5.8 ± 2.1 (6) n=15	6.1 ± 1.3 (6.2) n=62
BASFI	NA	5.5 ± 2.6 (6) n=13	6.2 ± 1.9 (6.4) n=32
HAQ	0.96 ± 0.39 (0.88) n=121	0.87 ± 0.46 (0.88) n=54	0. 9 ± 0.6 (0.8) n=8
Treatment			
Previous bDMARDs use, n (%)	**91 (55)**	**49 (60)**	**56 (70)**
1	38 (23)	18 (22)	14 (17.5)
2	21 (13)	22 (27)	20 (25)
≥3	32 (19)	9 (11)	22 (27.5)
Concomitant csDMARDs, n (%)	**144 (87)**	**71 (87)**	**43 (54)**
csDMARD monotherapy	133	59	43
MTX	*102*	*46*	*38*
LEF	*29*	*13*	*1*
HCQ	*2*		
SSZ			*4*
csDMARD combination	11	12	0
MTX+LEF	*5*		
MTX+HCQ	*4*		
MTX+LEF+HCQ	*1*		
LEF+HCQ	*1*		
MTX+CsA		*11*	
MTZ+SSZ		*1*	
GLM monotherapy, n (%)	**22 (13)**	**11 (13)**	**37 (46)**
Corticosteroid use, n (%)	**81 (49)**	**15 (18)**	**8 (10)**
Follow-up, months	22.6 ± 15.7 (18)	20.7 ± 15 (15)	22.7 ± 14.8 (20.8)

RA: rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; bDMARD: biologic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic DMARDs; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; CsA: cyclosporine; GLM: golimumab; NA: not applicable.

(40.2±1.98 months, p=0.067) and was significantly higher compared to PsA (34.1±2.53 months, p=0.01) patients (Fig. 1). No difference in GLM SOD was noticed between RA and PsA patients (p=0.204). The estimated SOD rates (by Kaplan-Meier analysis) for the whole patient population was 80%, 68% and 62% at 12, 24 and 36 months, respectively (Suppl. Table II).

SOD across different diagnoses

In the RA cohort, the overall GLM SOD was 58% at the end of the follow-up and did not differ between bDMARD-naïve and -experienced patients (p=0.87, Fig. 3A), as well as between patients receiving concomitant csDMARDs or not (p=0.392, data not shown). In contrast, SOD was marginally better in seropositive (RF+ and/or anti-CCP+) compared to seronegative patients (p=0.052, Fig. 3B). Interestingly, in multivariate Cox regression analysis of baseline variables, seropositivity was marginally associated with a decreased hazard ratio (HR=0.5, 95% confidence intervals (CI) =0.25–1.1, p=0.05) for drug discontinuation (Table II). Regarding other baseline factors, only a high VAS global score was associated with a higher risk for GLM discontinuation (HR=1.23, CI=1.01–1.50, p=0.04).

Concerning PsA patients, at the end of follow-up, 55% of patients were still on GLM without significant difference between bDMARD-naïve and experienced patients (p=0.98, Fig. 3C), or among those with or without concomitant csDMARD administration (p=0.218, data not shown). By multivariate analysis, a high SJC at baseline was associated with an increased risk (HR=1.1, 95% CI=1.00–1.21, p=0.04) while a high ESR were associated with a decreased risk (HR=0.98, 95% CI=0.96–0.99, p=0.02, Table II) for drug discontinuation.

AS patients treated with GLM showed the highest SOD (72%) compared to the other two groups at the end of the follow-up period. Similarly to RA and PsA patients, there was no effect in GLM SOD according to previous exposure to bDMARDs (p=0.76, Fig. 3D) or co-administration of csDMARDs (p=0.672, data not shown). Only a high VAS score at baseline was associated with higher discontinuation rate by multivariate analysis (HR=2.2, 95% CI=1.05–4.61, p=0.04, Table II).

Safety

The entire cohort was followed for a total of 606 patient-years (Table II). During the follow-up period, 104 adverse events (AEs) were recorded in 72 patients (22%), resulting in an incidence AE rate of 17/100 patient-years (Table III). The number and rate of serious AEs were 14 and 2.3/100 patient-years respectively, that occurred in 13 patients (4%). The mean time to an AE was 11.1±9.3 months (median: 8.4 months). The rate of infections in total and serious infections were 7.8/100 patient-years and 1.0/100 patient-years, respectively (Table III). There were 12 hospitalisations (comprising 11% of the total adverse events) with an incidence rate of 2.0/100 patient-years.

Only 11 patients (3.3%) discontinued treatment due to AEs (15.2% among those with an AE). Almost half (5/11, 45%) were due to infections, mainly involving the respiratory tract (4/5, 80%).

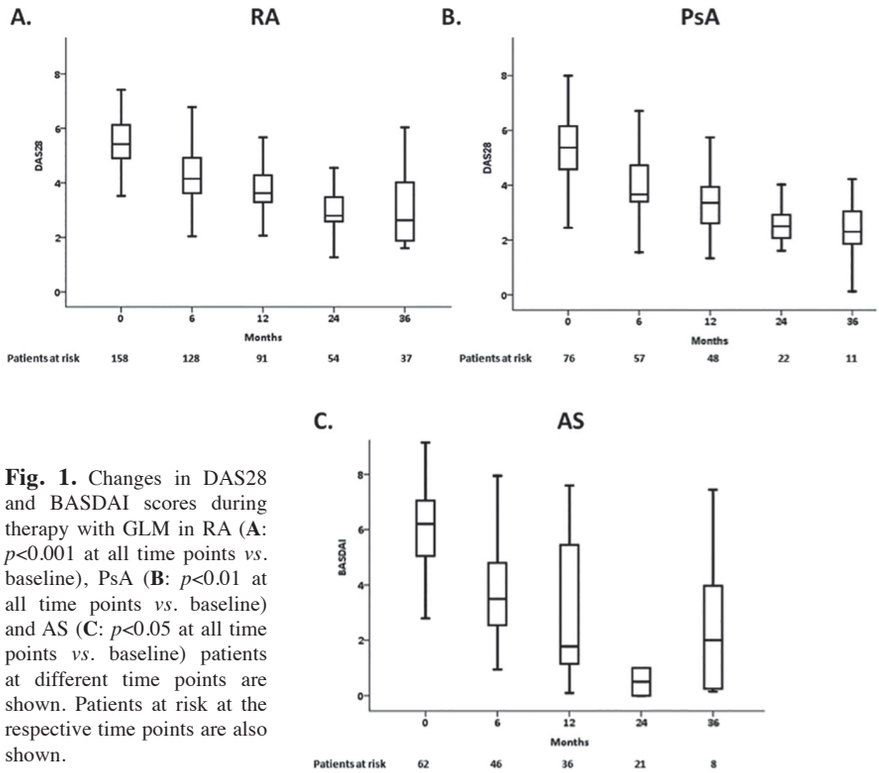

Fig. 1. Changes in DAS28 and BASDAI scores during therapy with GLM in RA (**A**: $p<0.001$ at all time points *vs*. baseline), PsA (**B**: $p<0.01$ at all time points *vs*. baseline) and AS (**C**: $p<0.05$ at all time points *vs*. baseline) patients at different time points are shown. Patients at risk at the respective time points are also shown.

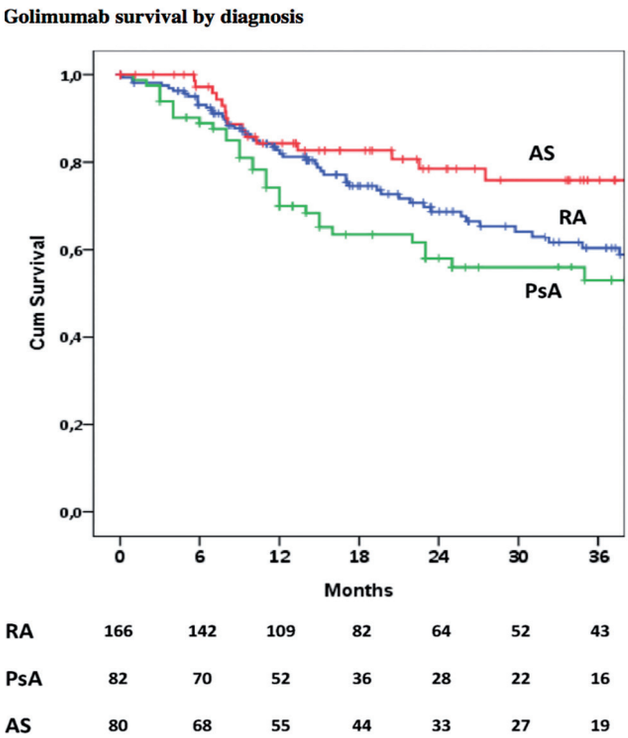

Fig. 2. The survival of GLM during 3 years of follow-up in rheumatoid arthritis (RA, blue solid line), psoriatic arthritis (PsA, green solid line) and ankylosing spondylitis (AS, red solid line) patients is shown in a Kaplan-Meier analysis. AS *vs*. PsA, $p=0.01$, AS *vs*. RA, $p=0.067$, RA *vs*. PsA $p=0.204$ (by log rank test).

No deaths or cases of malignancies, opportunistic infections or tuberculosis were recorded during follow-up.

Discussion

This is one of the few studies in the literature exploring the long-term GLM survival in daily clinical practice across all its approved indications for chronic inflammatory arthritides. Our results demonstrate that the drugs' clinical efficacy and safety in real life settings was comparable to that reported in RCTs and their TES with a high estimated survival rate of 68% and 62% at the end of the 2nd and 3rd year respectively.

In RA, the efficacy and safety of GLM has been demonstrated in RCTs which included patients who had failed cs-DMARDs (11) or anti-TNFs (12). In their TES, at approximately the same time points of our study (40 months or ~3.3 years), the drug's survival ranged from 51% (anti-TNF experienced patients) to 74% (bDMARD-naïve patients) (13). Two recent studies from Finland (8) and Italy (10) reported a 63-64% survival rate at 2 years which was slightly lower to that observed in our cohort (69%) at the same time point.

In contrast to the TES of the RCTs (13-17), we did not observe any difference in drug survival between bDMARD-naïve and experienced RA patients; of note, more than half of our patients had been previously exposed to bDMARDs. Similar results were reported in the ROB-FIN study, where there was only a non significant difference in drug survival at 3 years between the groups of anti-TNF naïve and experienced patients (65% *vs*. 60% respectively) (8) and the Italian study where although there bDMARD-naïve patients had a better drug survival at 2 years (76%) compared to the experienced patients (53%), the difference was again not statistically significant (10).

For "older" anti-TNFs such as adalimumab, etanercept or infliximab, in previous studies (18, 19) and in the report from the Hellenic Registry of Biologics (HeRBT), prior discontinuation of anti-TNFs was an independent predictor of anti-TNF failure.(20) Should the above mentioned finding be confirmed in other studies for GLM in RA it could differentiate it from other anti-TNFs.

The issue of anti-TNF drug survival according to the co-administration of csDMARDs has been addressed in different studies. Data from the HeRBT and other registries have shown a significant positive effect of combination therapy (mainly with MTX) in RA patients treated with the "older" anti-

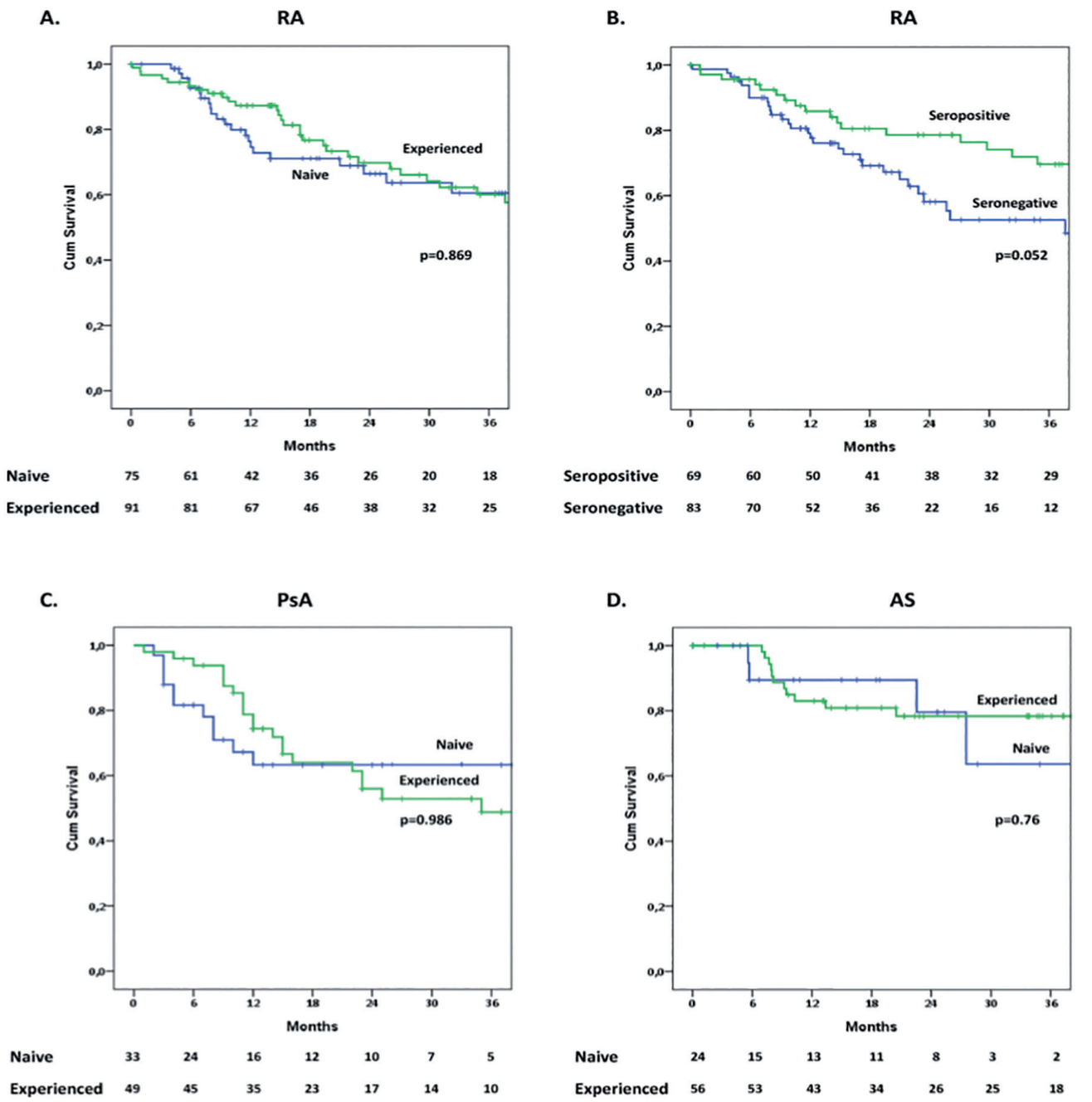

Fig. 3. The survival of golimumab (GLM) up to 3 years of follow-up in biologic disease-modifying anti-rheumatic drug (b-DMARD) naïve (blue solid line) and experienced (green solid line) RA (**A**), PsA (**C**) and AS (**D**) patients with the respective *p*-values (by log rank test) is depicted. Similarly, the drug survival among seropositive (green solid line) and seronegative (blue solid line) RA patients is shown (**B**).

TNFs (5, 20). In the ROB-FIN study which also included GLM, MTX use in combination with anti-TNFs was also associated with lower risk for drug discontinuation (HR=0.76) compared to anti-TNF monotherapy, although no specific data were given for GLM (8). Similarly to our study, Iannnone *et al*. did not identify csDMARD co-administration as a predictor for drug discontinuation (10).

For the first time, we observed that seropositive patients (RF and/or anti-CCP+) had a rather longer SOD compared to seronegative ones. Of note, seropositivity was also the only baseline factor marginally associated with decreased risk for drug discontinuation by multivariate analysis (HR=0.5, p=0.05). Although in the RCTs and the recent Finnish study, 72-85% of patients were RF+ (8, 11, 12), no data were reported regarding its potential effect on drug survival. A recent meta-analysis has shown no effect of seropositivity on the drug survival of "older" anti-TNFs (21). Certainly, more studies are needed in order to confirm our preliminary findings in our patient population.

In a recent systematic review and meta-analysis of drug registries and health care databases, the survival of the "older" anti-TNFs (adalimumab,

Table II. Uni- and multi-variate Cox regression analysis of different baseline variables associated with drug discontinuation during follow-up. In univariate analysis column, variables included in the multivariable model are shown in bold. In multivariate analysis, variables with *p*-value <0.1 are shown in bold and italic.

A. Rheumatoid arthritis (n=166)

Variable	Univariate analysis					Multivariate analysis**			
	n*	HR	95% C.I. Upper	Lower	*p*	HR	95% C.I. Upper	Lower	*p*
Sex, male	166	**0.43**	**0.13**	**1.39**	**0.16**	0.21	0.03	1.57	0.13
Age	165	1.00	0.98	1.02	0.98	0.99	0.97	1.02	0.62
Disease duration	166	0.99	0.96	1.03	0.73				
Seropositivity (RF/anti-CCP)	152	**0.56**	**0.31**	**1.01**	**0.05**	***0.50***	***0.25***	***1.10***	***0.05***
Previous bDMARD exposure	166	0.95	0.55	1.66	0.87				
Concomitant csDMARDs	166	1.49	0.59	3.75	0.39				
Concomitant corticosteroids	166	**0.72**	**0.42**	**1.25**	**0.25**				
Tender joint count (TJC)	158	**1.07**	**1.00**	**1.14**	**0.01**				
Swollen joint count (SJC)	158	**1.04**	**0.98**	**1.10**	**0.03**				
ESR	159	**0.98**	**0.97**	**0.99**	**0.04**				
VAS global (per 10 mm)	159	**1.23**	**1.05**	**1.44**	**0.01**	***1.23***	***1.01***	***1.50***	***0.04***
HAQ	121	**1.96**	**0.80**	**4.75**	**0.14**				

Data available from: * n (number) of patients **n=117 patients.

B. Psoriatic arthritis (n=82)

Variable	Univariate analysis					Multivariate analysis**			
	n*	HR	95% C.I. Upper	Lower	*p*	HR	95% C.I. Upper	Lower	*p*
Sex, male	82	**0.77**	**036**	**1.67**	**0.51**	0.56	0.23	1.36	0.20
Age	82	**1.02**	**0.99**	**1.05**	**0.26**	0.98	0.94	1.02	0.42
Disease duration	82	1.01	0.96	1.07	0.57				
Previous bDMARD exposure	82	0.99	0.48	2.07	0.99				
Concomitant csDMARDs	82	**2.34**	**0.56**	**9.79**	**0.24**				
Concomitant corticosteroids	82	**2.13**	**1.00**	**4.51**	**0.05**				
Tender joint count (TJC)	78	1.02	0.97	1.09	0.38				
Swollen joint count (SJC)	78	**1.08**	**1.00**	**1.18**	**0.05**	***1.10***	***1.00***	***1.21***	***0.04***
ESR	77	**0.98**	**0.96**	**1.00**	**0.04**	***0.98***	***0.96***	***0.99***	***0.02***
VAS global (per 10 mm)	77	**1.29**	**1.06**	**1.57**	**0.01**				
HAQ	54	1.47	0.59	3.69	0.40				

Data available from: * n (number) of patients ** n=76 patients.

C. Ankylosing spondylitis (n=80)

Variable	Univariate analysis					Multivariate analysis**			
	n*	HR	95% C.I. Upper	Lower	*p*	HR	95% C.I. Upper	Lower	*p*
Sex, male	80	**0.49**	**0.16**	**1.43**	**0.19**	0.29	0.05	1.82	0.19
Age	80	**0.99**	**0.95**	**1.04**	**0.70**	0.92	0.84	1.01	0.07
Disease duration	80	1.00	0.94	1.07	0.88				
Previous bDMARD exposure	80	0.83	0.26	2.63	0.76				
Concomitant csDMARDs	80	1.25	0.44	3.51	0.67				
Peripheral disease	57	**0.52**	**0.17**	**1.55**	**0.24**				
ESR	74	1.00	0.98	1.02	0.98				
VAS (per 10 mm)	46	**1.51**	**0.94**	**2.41**	**0.08**	***2.2***	***1.05***	***4.61***	***0.04***

Data available from: * n (number) of patients ** n=35 patients.

CI: confidence intervals; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; bDMARD: biologic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic DMARDs; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; VAS: visual analogue scale; HAQ: health assessment questionnaire.

etanercept, infliximab) in RA patients at 2 and 3 years ranged between 58–65% and 54–65%, respectively (5). In the HeRBT registry, the respective survival of these 3 anti-TNFs was 64-68% and 56–62% at 2 and 3 years, respectively (20). Overall, despite the limitations of an indirect comparison, our study shows a comparable long-term survival of GLM in RA to what has been previously reported for "older" anti-TNFs in real world settings.

Table III. Cumulative safety data for the entire patient population (n=328) during the follow-up period.

Side effects during Golimumab therapy in the entire patient population	
Side effects	
n	**328**
Patient-years (FU)	606
Adverse events (AEs), n	104
AEs/100 patient-years	17
Serious AEs, n(%)	14 (13.4%)
Serious AEs/100 patient-years	2.3
Hospitalisations, n(%)	12 (11%)
Hospitalisations /100 patient-years	2
Infections, n(%)	47 (45%)
Infections /100 patient-years	7.8
Serious infections/100 patient-years	1

FU: follow-up.

There are only few data regarding the long-term survival of GLM in PsA patients.(9, 10, 22-24) In the TES (22-24) of the initial RCT (25), 83% of patients were still on GLM at 2 years(23) and 70% at 5 years. (24) In the two recent real life studies from Finland (9) and Italy (10), the estimated drug survival at 2 years ranged between 64–67%(9, 10) and at 3 years it was 63% (9). In our study, the estimated drug survival was lower at 58% and 53% at the same time points. We did not observe any differences in drug survival between bDMARD-naïve or -experienced patients as well as between csDMARD co-treated or not patients. Similar findings were noted in the recent Italian study by Iannone *et al*. (10). Interestingly, a high ESR at baseline was associated with a decreased risk for drug discontinuation (HR=0.98, p=0.02), whereas a high baseline SJC was associated with an increased risk for drug discontinuation (HR=1.1, p=0.02).

These HRs though were based on a rather limited number of patients and their clinical significance is unclear at the moment.

There have not been any published long-term registry data for GLM-treated PsA patients so far (26). The survival of the other anti-TNFs in well-established PsA patients' registries, ranges between 57–75% at 2 years (27-30) and 59–64% at 3 years (28, 29, 31), which are similar or slightly higher to what we have observed in our GLM cohort. To compare with data from the population of Greece, the 3-year drug survival for the older anti-TNFs was estimated at 67% (Sidiropoulos P *et al*., manuscript submitted).

Regarding GLM survival in AS patients, in the TES of the initial RCT of GLM, the SOD rate was 81% (33) and 72% (34) at 2 and 5 years, respectively (32). In our study the estimated GLM survival at 2 and 3 years was 79% and 76%, respectively. Similarly, Iannone *et al*. reported a drug survival of 78% at 2 years. Only a high VAS score at baseline was associated with a higher risk for drug discontinuation by multivariate analysis, while again we did not observe any difference between bDMARD-naïve and -experienced patients.

For other anti-TNFs, data from observational cohorts and patient registries, have shown a survival rate of 60–75% at 2 (35-40) and 69% at 3 years (31). Interestingly, analysis of Greek AS patients in the HeRBT registry showed that the drug survival at 2 and 3 years for the older anti-TNFs was 78% and 71% respectively (Sidiropoulos *et al*., manuscript submitted). Collectively, our data may indicate a better long-term survival of GLM compared to other anti-TNFs in AS patients.

The clinical efficacy of GLM, as assessed by the recorded changes in commonly used indices of disease activity such as the DAS28 and BASDAI scores, was similar to what has been previously reported in RCTs and registry studies of the these 3 diseases. In RA, at the end of follow-up period almost half of patients still on therapy with evaluable data were in disease remission (46%), indicative of the long-term clinical efficacy of the medication on patients continuing treatment.

Regarding GLM's safety profile, its overall profile seems comparable to what has been reported in the respective RCTs and their TES. (4) More specifically, in our study, drug discontinuation due to AEs occurred in 3.3% of patients overall compared to 15% in the pooled analysis of 2228 patients treated with GLM in the TES for 5 years. (4) The rate of serious infections was lower in our study (1.0/100 patient-years) compared to the TES of GLM (3.29/100 patient-years) (4) and to other anti-TNFs (2.1-4/100 patient-years) (20) or rituximab (2.53/100 patient-years) (41) in Greek RA patients.

Limitations of our study include its retrospective design, absence of data concerning psoriatic skin involvement, potential differences in clinical practices between clinicians regarding bDMARD use, lack of data on comorbidities which may have influenced drugs' response and overall survival. Moreover, completeness of data mostly in reference to clinical efficacy is always an issue in observational studies and this was also the case in our study.

In conclusion, this is one of the largest studies in the literature evaluating the long-term efficacy and safety of GLM in real life settings across all its approved indications. The study shows a comparable drug survival to other anti-TNFs with a low rate of discontinuations due to AEs. Furthermore, for the first time we have observed that seropositivity was associated with a lower rate for drug discontinuation in RA patients, a finding that needs to be explored further in future trials.

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