Real-world effectiveness of golimumab in the treatment of patients with active rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis who failed initial TNF-α inhibitor therapy: a pooled analysis of European prospective observational studies (the GO-BEYOND program)

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Abstract

Objective
Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) patients often experience secondary non-response to a first-line tumour necrosis factor alpha inhibitor (TNFαi). This pooled analysis of six observational studies in Europe (GO-BEYOND program) provides an estimate of second-line golimumab (GLM) effectiveness for these rheumatic diseases.

Methods
The GO-BEYOND studies included common disease-specific endpoints allowing for a pooled analysis. Patients had discontinued one prior TNFαi (due to loss of efficacy, tolerability, or inconvenience) and were followed for 12 months after GLM initiation. Primary endpoints included the proportion of patients achieving low disease activity (LDA, DAS28-CRP<3.2) in RA, minimal disease activity (MDA, fulfilment of 5 of 7 outcome measures) in PsA, or low disease activity (ASDAS<2.1) in axSpA at 6 months. Disease activity at 3 and 12 months and quality of life (QoL; EQ-5D-3L) were also assessed. Adverse events were monitored. Protocol-specified analyses were based on observed data.

Results
In 712 patients, (n=325, RA; 186, PsA; 201, axSpA), mean age was 54 years, 64% were female, and median disease duration was 5 years. Primary endpoints were achieved in 58.3% (RA), 45.5% (PsA), and 45.4% (axSpA) of patients; disease activity improvements were observed at 3 and 12 months and EQ-5D-3L results showed improved QoL over time. The treatment persistence rate at 12 months was 67.8% of patients. No new safety signals were observed.

Conclusion
This pooled analysis of the GO-BEYOND studies showed that treatment with GLM was effective and represented a valid second-line option for RA, PsA, and axSpA patients.

Key words
TNF-α inhibitor, second-line therapy, rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, real-world evidence, effectiveness, second-line biologic, golimumab

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Introduction

Chronic inflammatory arthritis disorders such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) are chronic inflammatory autoimmune conditions, sharing key pathophysiological mechanisms (1). Tumour-necrosis factor alpha inhibitors (TNFαis) are important treatment options for patients with chronic inflammatory arthritis (2), and lifelong treatment is required to control symptoms. It has, however, been estimated that 30% to 40% of RA, PsA, and axSpA patients treated with an initial TNFαi discontinue treatment and require switching to another treatment (3-5). Among other factors, advanced disease progression, the presence of antibodies against the applied TNFαi, and decreased therapy adherence, are potential causes for secondary loss of efficacy (6, 7). Patients also may stop a first TNFαi due to individual tolerability issues or dissatisfaction. A switch to a different TNFαi, which avoids moving to a different drug class with another safety profile, might be a successful option for secondary non-responding patients, an approach that is supported by the European League Against Rheumatism (EULAR) recommendations for disease management (3-5, 8-10).

Golimumab (GLM) is a high-affinity human immunoglobulin monoclonal antibody forming stable complexes with the human TNF-α, thereby preventing the binding of TNF-α to its receptors (11). The efficacy and safety of GLM, as a first line TNFαi therapy, have largely been demonstrated in randomised controlled trials of patients with RA, PsA, and axSpA (10, 12, 13). Additionally, the GO-AFTER trial showed that RA patients who had discontinued a previous TNFαi due to lack of effectiveness responded better to GLM than placebo (14).

The GO-BEYOND program included six prospective, observational studies that were conducted across multiple European countries to evaluate the real-world effectiveness of GLM in patients with an inadequate response to a previous TNFαi for the treatment of active RA, PsA, or axSpA. Here, we report on a prospective pooled analysis of data from these studies, to provide a more precise estimate of GLM effectiveness for each of these rheumatic diseases.

Methods

Program design

The GO-BEYOND program consisted of national, multi-centre non-interventional studies conducted prospectively in 6 European countries (Belgium, Bulgaria, France, Germany, Greece, and Italy) in a total of 144 centres (including rheumatology private practices and hospital services) from March 2017 to February 2021. The studies were consistent with the EU Directive 2001/20/EC section for non-interventional studies where GLM was prescribed in accordance with the terms of the marketing authorisation and summary of product characteristics: the assignment of patients to a particular treatment regimen was not defined by the observational plan and was the responsibility of the treating physician, and no extra means of interventions that would not otherwise be used were applied.

These studies were prospectively planned and designed to be pooled, including the evaluation of disease-specific outcomes by indication. Patients who were prescribed GLM (Visit 0/Baseline Visit) were enrolled. A minimum of three follow-up visits over 12 months were scheduled: Visit 1 at 3 months, Visit 2 at 6 months, and Visit 3 at 12 months after the date of the first injection of GLM. In each country, the study results were collected in an electronic Case Report Form (eCRF). Therefore, in accordance with a prespecified statistical analysis plan, we conducted a pooled analysis of structured data from these studies. Before pooling the data into a single database, a global analysis of consistency between protocols, eCRFs and databases was performed. The data extraction from initial datasets and the resulting pooled database was fully documented in terms of methods used for extraction, number of subjects and number of variables (including type, format and labels).

As no new data were collected, this pooled analysis study did not require submission to an Institutional Review Board/Independent Ethics Committee.

All patients provided written, informed consent in each individual country study.

Patients

The GO-BEYOND studies enrolled men or women 18 years of age or older with a diagnosis of active RA (moderate to severe), PsA (active and progressive), or axSpA (severe and active), who were being considered for treatment with GLM. Participants must have been previously treated with one initial TNFαi (adalimumab, certolizumab pegol, etanercept, or infliximab) for at least a full first cycle. The initial TNFαi must have provided an initial treatment response, and the patient must have stopped treatment due to TNFαi failure based on loss of efficacy (secondary non-response), tolerability issues (*e.g.* injection-site reactions), or inconvenience (*e.g.* injection frequency).

Patients were excluded from the study if they had a contraindication to GLM, were treated with other non-TNFαi biologics or more than one TNFαi, were primary TNFαi non-responders (patients who did not show any or little improvement upon an initial TNFαi), were participating in another trial with an investigational agent, or had previously received GLM as first-line therapy.

Study endpoints

The primary endpoint for this pooled analysis was assessed at the end of month 6 after initiation of GLM treatment, as follows: 1) RA: the proportion of patients who achieved Low Disease Activity (LDA) according to the Disease Activity Score for 28 joints based on C-reactive protein [DAS28-CRP] <3·2 (15); 2) PsA: the proportion of patients who achieved Minimal Disease Activity (MDA), which entailed fulfilment of five of seven MDA criteria (16); and 3) AxSpA: the proportion of patients who achieved LDA (Ankylosing Spondylitis Disease Activity Score based on C-reactive protein [ASDAS-CRP] <2.1) (17, 18).

Secondary endpoints in RA and PsA patients included the following: the percentage of patients who achieved Low Disease Activity (DAS28-CRP <3.2) at the end of months 3 and 12 after initiation of GLM; the percentage of patients

achieving good or moderate EULAR response (19) at 3, 6 and 12 months; the percentage of patients who reached remission (DAS28-CRP <2.6) at the end of months 6 and 12 after initiation of GLM. Additionally, in PsA patients, the percentage of patients who achieved MDA at the end of 3 months and 12 months after initiation of GLM.

In axSpA patients, secondary endpoints included the following: percentage of patients who achieved LDA (ASDAS <2.1) at the end of months 3 and 12 months after initiation of GLM; the percentage of patients who achieved inactive disease (ASDAS <1.3) at the end of months 6 and 12 months after initiation of GLM; the percentage of patients who achieved BASDAI 50 at the end of months 3, 6 and 12 after initiation of GLM (20, 21).

Quality of life (QoL) was also a secondary endpoint and was measured with EQ-5D-3L (an outcome that consists of five domains and a visual analogue scale [VAS]) at baseline, 6 and 12 months after initiation of GLM (22).

Exploratory endpoints included evaluation of the Patient Acceptable Symptom State (PASS) (23), persistence (*i.e.* the proportion of patients remaining on GLM), and extra-articular manifestations (EAMs) at 3, 6 and 12 months.

Safety evaluation

The safety datasets from each individual study were pooled and the relevant safety information summarised accordingly. As this was a pooled analysis of previously collected data for which safety events had already been appropriately reported, no additional reporting of individual adverse events was required or performed.

Statistical methods

This was an analysis of six prospectively pooled observational studies that was conducted in accordance with a prespecified statistical analysis plan. While the study evaluated the statistical significance of changes from baseline for 3 disease indications, these analyses should be considered exploratory or descriptive in nature as both this pooled analysis and the original individual-country studies were all single arm.

Categorical data, including categories of continuous data, are presented in frequency tables. Continuous data are presented using the median value and 25 (Q1) and 75 (Q3) percent quartiles and/or mean and standard deviation. Continuous variables were described by visit and as change from baseline per time of analysis, if applicable. In the inferential analyses, p-values <0.05 were considered statistically significant. Due to the observational and exploratory nature of the study, no adjustment for multiple testing was applied.

Patients were followed for up to 12 months, with protocol-specified analyses based on observed data reported (*i.e.* the sub-populations of patients with available data for each endpoint). For these analyses, missing data were neither replaced nor extrapolated. A more stringent, supportive analysis using non-responder imputation (NRI), for which missing data were imputed as a non-response, was also performed for the primary endpoint.

A multivariate logistic regression (backward regression model) was performed to evaluate the impact of predictive variables (age, sex, smoker status, BMI, active pathology, reasons for switch from initial TNFαi, disease duration, prior TNFαi treatment, EAMs and comorbidities) on the primary endpoint. A univariate logistic regression model was used first to examine the association between each clinical/pathological parameter and response (yes/no). Any variable with a p-value ≤0.20 in the univariate analysis and with less than 20% of missing data was then included in the multivariable logistic regression model. Patients with missing data were considered non responders. All statistical tests were two-sided and p<0.05 was considered as statistically significant. IBM SPSS Statistics (v. 27.0 and eventual updates/upgrades) and StatXact (v. 6.0) were used for the statistical analyses.

Results

Patients

A total of 712 patients were enrolled across six studies (Belgium n=86; Bulgaria n=33; France n=107; Germany n=50; Greece n=242; Italy n=194).

Of those, 325 had RA, 186 had PsA, and 201 had axSpA. Baseline patient characteristics were relatively balanced across indications with a mean (SD) age of 54.2 (13.0) years where the RA population was older (57.9 [12.6] years) than the axSpA (49 [13.2] years) and PsA (53.3 [11.2] years) populations. A higher proportion of patients were female (63.8%) compared with male (36.2%), mean (SD) BMI was 27.5 (5.4) kg/m², and mean (SD) disease duration was 8.6 (8.8) years. The most common prior TNFαi therapies were etanercept (41.6%) and adalimumab (31.7%). The most common reason for switching was loss of efficacy (76.8%) followed by tolerability/safety issues (11.7%) (Table I).

A total of 560/712 (78.7%) patients were on at least one concomitant therapy at baseline, with a higher proportion among RA patients (302/325 [92.9%]), compared with PsA (131/186 [70.4%]), and axSpA (127/201 [63.2%]) patients. The most common concomitant medication classes were conventional synthetic DMARDs (388/712 [54.5%]) followed by corticosteroids (188/712 [26.4%]), and NSAIDs (157/712 [21.1%]).

Among 527 patients for whom an assessment was performed, 395 (75%) had at least one comorbidity at baseline. At baseline, median DAS28-CRP was 4.6 in RA patients and 4.5 in PsA patients. In axSpA patients, median AS-DAS-CRP was 3.4 and median BAS-DAI was 6.

Effectiveness of GLM
The proportions of patients who achieved the primary endpoints at 6 months among RA patients (DAS28-CRP<3.2), PsA patients (fulfilment of 5 of 7 outcome measures for MDA), and axSpA patients (ASDAS<2.1) were 58.3% (n/N=127/218), 45.5% (n/N=60/132), and 45.5% (n/N=59/130), respectively (Fig. 1). A supportive, more stringent, Non-Responder Imputation (NRI) analysis confirmed GLM effectiveness in this difficult-to-treat, refractory population, with approximately one-third of patients achieving the primary endpoint: 39.1% (n/N=127/325) in RA, 32.3% (n/N=60/186) in PsA, and 29.4% (n/N=59/201) in axSpA (Fig. 1).

Table I. Baseline characteristics.

	RA n=325	PsA n=186	axSpA n=201	Total n=712
Sex				
Female	253 (77.8%)	100 (53.8%)	101 (50.2%)	454 (63.8%)
Age				
Mean (SD), years	57.9 (12.6)	53.3 (11.2)	49.0 (13.2)	54.2 (13.0)
Range, years	19-88	24-82	19-77	19-88
≥65 years	100 (30.8%)	32 (17.2%)	29 (14.4%)	161 (22.6%)
BMI				
Missing data, n	8	2	3	13
Mean (SD), kg/m²	27.5 (5.7)	27.9 (5.4)	27.1 (5.0)	27.5 (5.4)
Range, kg/m²	16.9 - 54.4	18.9 - 51.9	17.6 - 50.2	16.9 - 54.4
Prior TNFαi therapy				
Missing data, n	7	8	10	25
Adalimumab	78 (24.0%)	72 (38.7%)	76 (37.8%)	226 (31.7%)
Certolizumab	34 (10.5%)	11 (5.9%)	22 (10.9%)	67 (9.4%)
Etanercept	162 (49.8%)	77 (41.4%)	57 (28.4%)	296 (41.6%)
Infliximab	44 (13.5%)	18 (9.7%)	35 (17.4%)	97 (13.6%)
Adalimumab – Etanercept*	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.1%)
Reason for switching from prior TNFαi therapy				
Secondary loss of efficacy	245 (75.4%)	150 (80.6%)	152 (75.6%)	547 (76.8%)
Tolerability issue or safety reason	35 (10.8%)	24 (12.9%)	24 (11.9%)	83 (11.7%)
Elective/other reason	45 (13.8%)	12 (6.5%)	25 (12.4%)	82 (11.5%)
Disease duration				
Missing data, n	1	1	0	2
Mean (SD), years	9.2 (9.4)	8.1 (7.2)	8.0 (9.3)	8.6 (8.8)
Disease activity				
Mean (SD) disease activity	DAS28-CRP: 4.5 (0.98)	DAS28-CRP: 4.2 (1.0)	ASDAS-CRP: 3.2 (0.97) BASDAI: 5.9 (1.9)	--

* One patient was reported to have been taking simultaneous adalimumab and etanercept prior to initiating treatment with GLM.

Secondary endpoints were supportive of the results shown with the primary endpoints, with improvements in disease activity consistently observed at 3, 6, and 12 months in each of the therapeutic indications (Table II).

QoL was assessed in all therapeutic indications using the EQ-5D-3L instrument. In the overall population, the mean (SD) EQ-5D-3L VAS score improved from 47.8 (20.3) at baseline, to 66.9 (19.46) at 6 months, and further to 70.5 (19.7) at 12 months. The changes of EQ-5D-3L VAS scores in each of the therapeutic indications are shown in Figure 2. The proportion of patients in each therapeutic indication who reported some or extreme problems for the individual dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression reduced at each time point during the 12-month follow-up, while the proportion of those who reported no problems increased over time (Supplementary Fig. S1).

For the exploratory patient-reported endpoint of PASS, the proportion of patients (% [n/N]) who reported being satisfied with their current health state was 21.9% (105/479) at baseline, 64.6% (281/435) at 3 months, 70.7% (273/386) at 6 months, and 74.2% (284/383) at 12 months (Suppl. Fig. S2).

At baseline, 33.9% (179/528) of patients had at least one EAM, with enthesitis and psoriasis being the most frequently reported ones, by 13.3% (69/520) and 21.0% (109/518) of patients, respectively. Presence of EAMs was highest in PsA patients, followed by AxSpA patients (Fig. 3). The proportion of patients with at least one EAM decreased to 25.1% (89/355) at 3 months, 23.9% (78/326) at 6 months, and 22.3% (59/265) at 12 months. Decreases over time were also shown in patients with axSpA and PsA (Fig. 3).

In the exploratory analysis of treatment persistence, the proportion of patients continuing to take GLM were
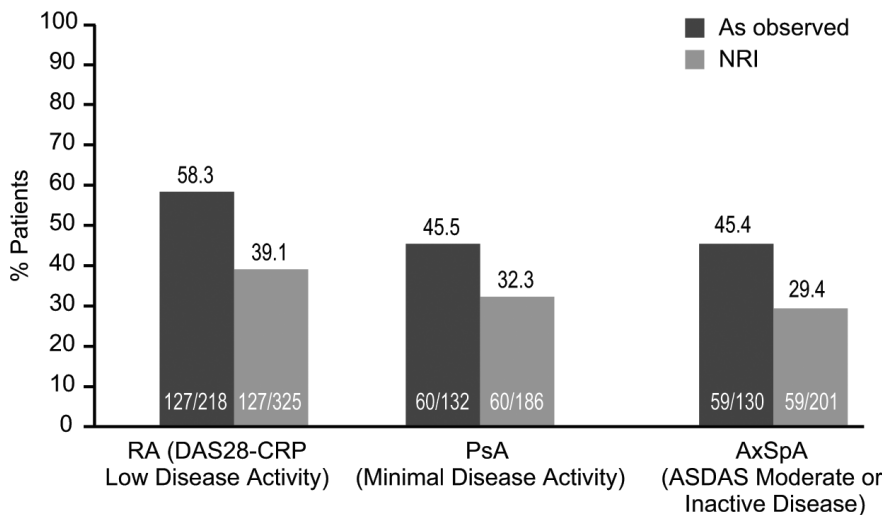
Fig. 1. Percentage of patients achieving low or minimal disease activity at 6 months (Primary Endpoints). NRI: non-responder imputation.

Table II. Percentage of patients achieving select secondary endpoints.

	3 months % (n/N)	6 months % (n/N)	12 months % (n/N)
RA patients			
LDA (DAS28-CRP<3.2)	43.1 (115/267)	58.3 (127/218)	63.6 (126/198)
Remission (DAS28-CRP<2.6)	27.7 (74/267)	40.8 (89/218)	47.5 (94/198)
EULAR Good or Moderate Response	65.1 (168/258)	75.6 (158/209)	82.1 (156/190)
PsA patients			
MDA (5 of 7 criteria)	28.1 (38/135)	45.5 (60/132)	57.6 (68/118)
LDA (DAS28-CRP<3.2)	55.4 (67/121)	71.4 (90/126)	78.5 (84/107)
Remission (DAS28-CRP<2.6)	32.2 (39/121)	60.3 (76/126)	68.2 (73/107)
EULAR Good or Moderate Response	73.9 (82/111)	80.2 (93/116)	82.0 (82/100)
axSpA patients			
ASDAS LDA (<2.1)	41.4 (60/145)	45.4 (59/130)	57.7 (79/137)
ASDAS Inactive Disease (<1.3)	13.8 (20/145)	20.0 (26/130)	24.1 (33/137)
BASDAI50	28.7 (47/164)	35.8 (54/151)	49.7 (77/155)

LDA: low disease activity; MDA: minimal disease activity; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI50: Bath Ankylosing Spondylitis Disease Activity Index (50% improvement in BASDAI score; Differences in N's between cohorts for different measures at the same timepoint are due to missing data for one or more outcomes.

84.7% (603/712) at 3 months, 73.9% (526/712) at 6 months, and 67.8% (483/712) at 12 months. In RA patients, 82.5% were still on treatment at 3 months, 67.7% at 6 months and 60.9% at 12 months. In axSpA patients, 82.1% were still on treatment at 3 months, 75.6% at 6 months and 70.6% at 12 months. In PsA patients, 91.4% were still on treatment at 3 months, 82.8% at 6 months and 76.9% at 12 months.

In the logistic regression analysis assessing prognostic impact of baseline characteristics, the final multivariate regression model was based on 501/712 patients (70.4%). In this population, overweight and obese patients were 2 times less likely to have a response than patients with normal BMI (OR: 0.546; 95% CI [0.35; 0.852], $p=0.0077$ and OR: 0.472; 95% CI [0.289; 0.770], $p=0.0026$, respectively). Similarly, axSpA and PsA patients were 2 times less likely to have a response than RA patients (OR: 0.525; 95% CI [0.326; 0.845], $p=0.0079$ and OR: 0.561; 95% CI [0.318; 0.989], $p=0.0458$, respectively). Patients with enthesitis were 2.5 times less likely to have a response than patients without enthesitis (OR: 0.396; 95% CI [0.199; 0.788], $p=0.0083$) whereas those with psoriasis were 2 times more likely to have a response (OR: 2.184; 95% CI [1.229; 3.880], $p=0.0077$).

Overall, 22.2% (158/712) of patients experienced an adverse event, with a higher proportion in RA (30.5% [99/325]) *vs*. PsA (12.9% [24/186]) and axSpA (17.4% [35/201]). The most frequently reported AE was drug ineffective (7.2% [51/712]), followed by infections and infestations (6.0% [43/712]). Serious AEs were reported by 4.4% (31/712) of patients, among which 1.1% (8/712) reported serious infections. There were no deaths reported during the course of these studies and no new safety signals were observed.

Discussion

The strategy of switching to a second-line TNFαi after treatment failure with a first-line TNFαi is supported by the European Alliance of Associations for Rheumatology (EULAR) recommendations for treatment of RA, PsA, and axSpA (9, 24, 25). The studies in the GO-BEYOND program were done to evaluate this strategy with GLM in a real-world setting in 712 chronic inflammatory arthritis patients participating in 6 studies across several countries in Europe (*i.e.* Belgium, Bulgaria, France, Germany, Greece, and Italy). The individual studies were prospectively planned to be pooled and were designed with similar inclusion criteria and common disease-specific endpoints to allow for increased statistical power and a more precise assessment of the effectiveness of GLM in this patient population (26-28). Data on the effectiveness of second-line TNFαi for patients and clinicians are important due to the changing clinical therapeutic landscape as new therapies are introduced and as biosimilar TNFαi become available worldwide.

The results of the GO-BEYOND pooled analysis showed that GLM was an effective second-line treatment of RA, PsA, or axSpA. A large proportion of patients achieved clinical response (LDA or MDA) in each condition in not only the primary as-observed analysis, but also the more stringent NRI analysis, where missing data were analysed as non-responders. These results demonstrate remarkable effectiveness considering the difficult-to-treat nature of this population of patients who experienced an initial treatment response
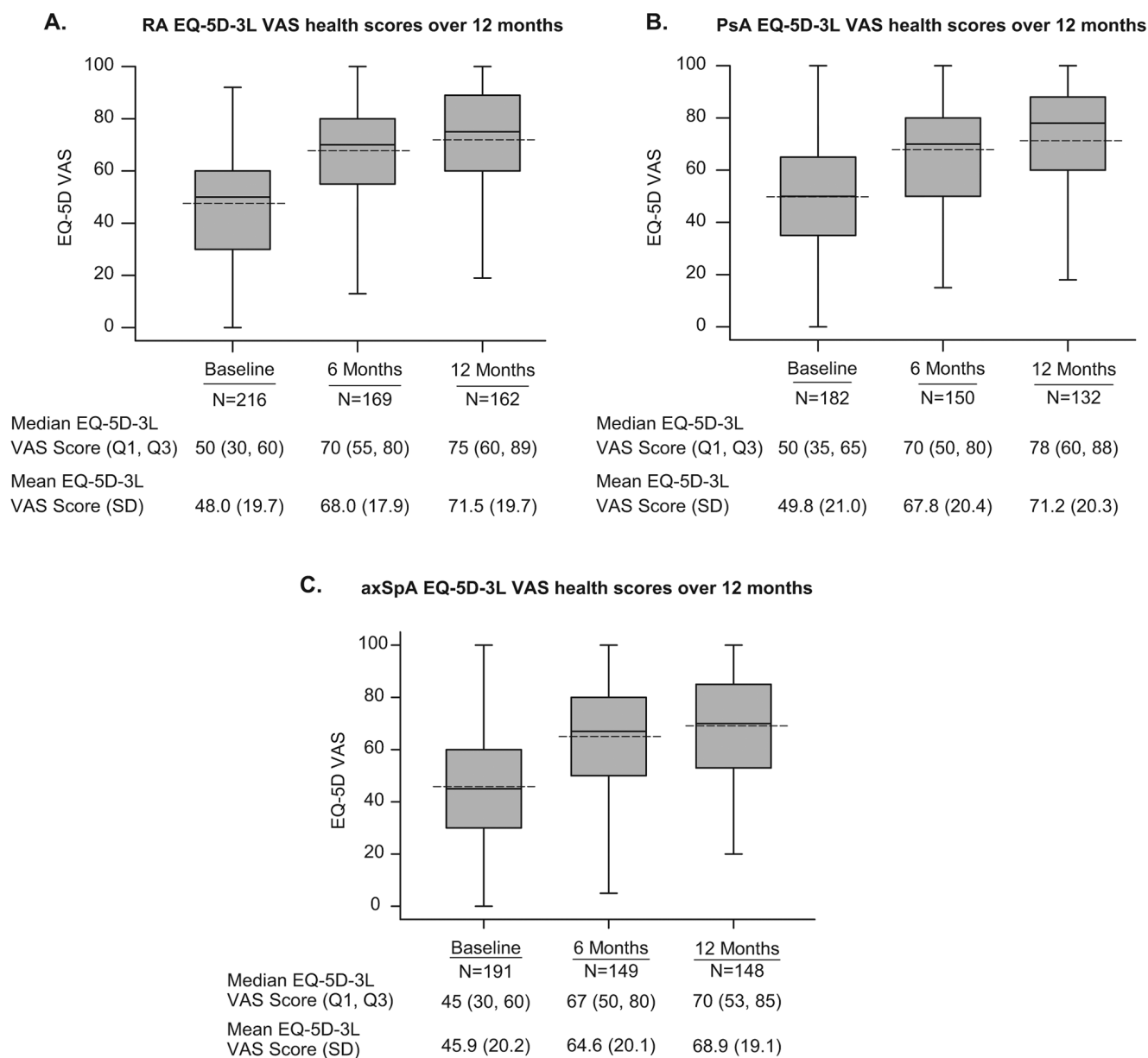
A.

RA EQ-5D-3L VAS health scores over 12 months

	Baseline N=216	6 Months N=169	12 Months N=162
Median EQ-5D-3L VAS Score (Q1, Q3)	50 (30, 60)	70 (55, 80)	75 (60, 89)
Mean EQ-5D-3L VAS Score (SD)	48.0 (19.7)	68.0 (17.9)	71.5 (19.7)

B.

PsA EQ-5D-3L VAS health scores over 12 months

	Baseline N=182	6 Months N=150	12 Months N=132
Median EQ-5D-3L VAS Score (Q1, Q3)	50 (35, 65)	70 (50, 80)	78 (60, 88)
Mean EQ-5D-3L VAS Score (SD)	49.8 (21.0)	67.8 (20.4)	71.2 (20.3)

C.

axSpA EQ-5D-3L VAS health scores over 12 months

	Baseline N=191	6 Months N=149	12 Months N=148
Median EQ-5D-3L VAS Score (Q1, Q3)	45 (30, 60)	67 (50, 80)	70 (53, 85)
Mean EQ-5D-3L VAS Score (SD)	45.9 (20.2)	64.6 (20.1)	68.9 (19.1)

Fig. 2. Evolution of EQ-5D-3L VAS Health Scores over 12 months in **A**) RA patients; **B**) PsA patients; and **C**) axSpA patients

on TNFαi, but had stopped treatment due to loss of efficacy, tolerability issues, or inconvenience. Effectiveness was demonstrated longitudinally, with patients achieving LDA or MDA in each condition starting as early as 3 months and through 12 months. Notably, remission or inactive disease are important goals in chronic inflammatory arthritis and were achieved in a large proportion of patients by 12 months (*i.e.* nearly half of RA patients, over two-thirds of PsA patients, and nearly a quarter of axSpA patients).

Treatment persistence is an important indicator of drug effectiveness and has been reported from multiple cohorts of patients with chronic inflammatory arthritis receiving treatment with GLM (29-34). Studies evaluating treatment persistence tend to show that biologic-naïve patients exhibit better drug survival compared with biologic-experienced patients, thus highlighting one of the challenges in treating patients with a prior treatment failure with a biologic (35-37). In the pooled analysis of the GO-BEYOND program, treatment persistence was evaluated as an exploratory endpoint and was observed in approximately two-thirds of patients continuing treatment after a year of therapy with GLM, which is a strong indicator of GLM effectiveness as a second-line TNFαi treatment.

Patient-reported outcomes using the PASS measurement in GO-BEYOND also demonstrated significant improvements from baseline by 3 months that were maintained up to 12 months in all three indications with regard to whether or not patients considered their current disease state to be satisfactory. These patient-reported outcomes are important components of patient satisfaction, which contributes to long-term treatment persistence. An additional exploratory endpoint included in this analysis
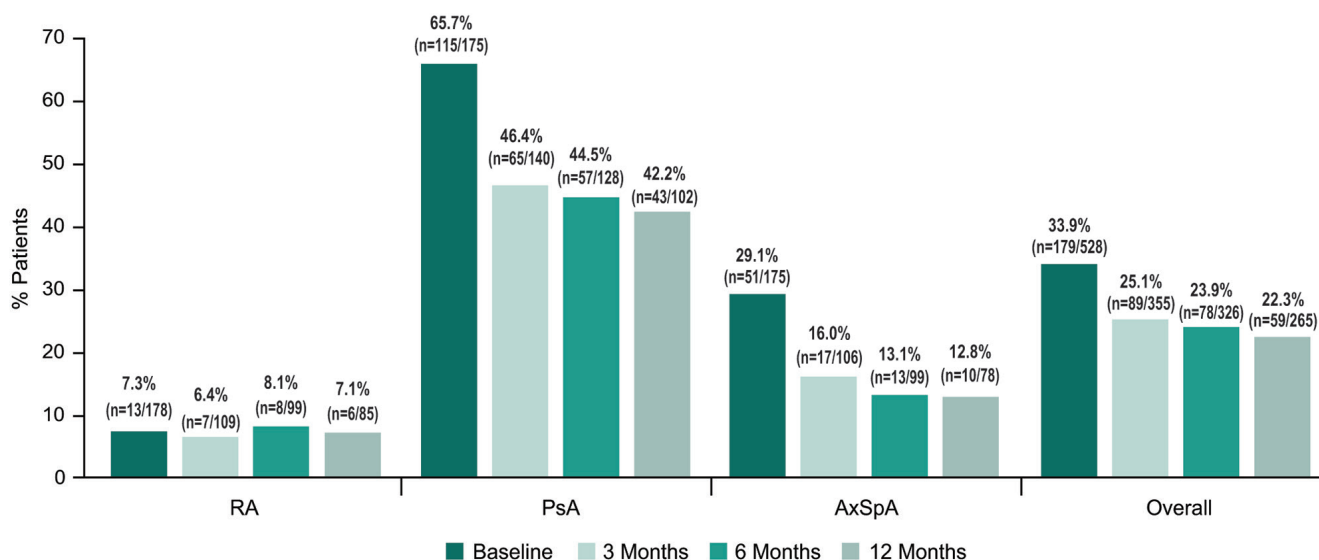
Fig. 3. Proportion of patients with extraarticular manifestations (EAMs) over time.

was the evaluation of EAMs, an important factor in the treatment of chronic inflammatory arthritis, particularly in PsA. In our pooled analysis of the GO-BEYOND program, the incidence of EAMs in PsA patients was reduced by 30% in patients with data from baseline to month 12. We also observed a 50% decrease in the incidence of EAMs in axSpA patients, although these results should be interpreted with caution due to the high number of patients for whom the EAMs assessment was not reported. Importantly, the results of this analysis of the GO-BEYOND program are generalisable to real-world populations as the patients included in the GO-BEYOND studies were typical for the rheumatic diseases evaluated with regard to demographics, previous first-line TNFαi, and reasons for switching. (28-32, 36, 37). A logistic regression analysis of the impact of multiple baseline patient characteristics on treatment response at 6 months showed that overweight or obese patients, patients with enthesitis, and SpA patients were less likely to have a treatment effect, whereas those with concomitant psoriasis were more likely to have a treatment effect. Additionally, the presence of broad demographics across the studies included in this pooled analysis allows for the observation of effectiveness in populations where special prescribing considerations might be necessary for chronic inflammatory arthritis. For example,

over 20% of patients were over the age of 65 years, a demographic for whom some treatment choices such as Janus kinase inhibitors are precluded or limited due to safety concerns; as such, data on second-line therapy to re-establish treatment response without changing mechanism of action are of particular importance. The logistic regression conducted in the overall pooled population of the GO-BEYOND program showed that age was not a significant variable impacting treatment response (38).

The effectiveness observed in this pooled analysis of the GO-BEYOND program is in line with what has previously been reported for patients experiencing benefit with GLM after treatment failure with a previous TNFαi or other biologics (28-32, 36, 37). In the GO-AFTER study, a Phase 3 randomised controlled trial evaluating GLM in patients with active RA despite previous treatment with TNFαi, ACR20 was achieved by up to 44% of participants by 24 weeks. LDA as determined by a DAS28 score <3.2 was assessed as a secondary endpoint using an NRI analysis in GO-AFTER and was achieved by 34% of patients in the combined GLM group, a similar rate to that observed in the current study (14). Real-World Evidence (RWE) studies have further supported the use of GLM as a second-line treatment in patients with RA, as well as PsA and AxSpA. Specifically, a *post-hoc* analysis of the

GO NICE observational study of patients with RA, PsA, or axSpA, showed strong treatment effects for second-line therapy relative to the subgroup of patients who were evaluated for first-line therapy (39, 40). The results of GO NICE in the patients receiving GLM as second-line therapy demonstrated a proportion of patients achieving remission of 41% in RA patients, a proportion of almost half of PsA patients achieving clinical response (as assessed with the Psoriatic Arthritis Response Criteria (PsARC) index), and important reductions in mean BASDAI scores in axSpA patients (39). Other RWE studies such as GO PRACTICE, research by Alegre-Sancho *et al*. and Scrivo *et al*., as well as analyses from the GISEA registry, showed important improvements in clinical outcomes in patients with these inflammatory arthritic disorders (35, 36, 30, 41). Health-related QoL improvements were demonstrated in the RWE studies, GO-NICE and GO-ART, that were consistent with EQ-5D-3L data in the GO-BEYOND pooled analysis (42, 43). These studies represent a large body of evidence that support the findings in the GO-BEYOND pooled analysis, which showed large proportions of patients achieving meaningful improvements in disease activity in populations of RA, PsA and axSpA patients who have experienced difficulties and setbacks with previous TNFαi treatments.

Accounting for limitations is important when assessing data from observational research. For the GO-BEYOND pooled analysis, one such limitation is missing data, which was an issue due to the observational nature of the individual studies and related loss of follow-up. Approximately 30% of patients had missing data for the primary endpoints, a proportion similar to previous observational studies (36, 39, 40). Another limitation was the lack of data on dose, which would have allowed evaluation of dosing strategies and treatment response. Consequently, analyses on treatment response based on dose as it relates to examined covariates such as body weight were not possible. Additionally, country-to-country variations were not considered as this analysis pooled data across six different countries. Notably, this analysis was descriptive in nature and any evaluation of statistical significance is exploratory, particularly since this was a single-arm pooled analysis of individual country-led studies. Finally, this analysis was unable to differentiate outcomes among subgroups of patients defined by reasons for discontinuation from first-line TNFαi therapy; similar to real-world settings, the vast majority of those patients who switched to second-line treatment was due to a loss of efficacy, thus making sample sizes for other reasons too small for analysis.

Nonetheless, this analysis included a large, prospective cohort of patients across several EU countries and evaluated different pathologies. The large sample size allowed for more precise estimate of effectiveness compared with the individual studies. Additionally, to mitigate the limitation regarding missing data, we conducted an NRI analysis for the primary endpoints, which confirmed the effectiveness at 6 months after initiating second-line treatment with GLM for RA, PsA, or axSpA.

In summary, this prespecified pooled analysis of six European studies in patients with active RA, PsA or axSpA who experienced secondary failure to an initial TNFαi showed that treatment with GLM was effective and represented a valid second-line option. A large proportion of patients on GLM achieved low or minimal disease activity at 6 months, which was associated with high rates of treatment persistence and improved quality of life during 12 months of therapy. Safety was consistent with the known safety profile of TNFαis with no new safety signals identified in this pooled analysis.

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