An observational prospective study on predictors of clinical response at six months in patients with active psoriatic arthritis treated with golimumab

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Abstract

Objective

Recently, research has been focused on the identification of predictors of response to treatment in patients with active psoriatic arthritis (PsA). The objective of this study was to develop a model to predict the clinical response at 6 months in patients with PsA starting the anti-tumour necrosis factor-α golimumab.

Methods

This prospective observational study explored a range of factors, including demographic data and baseline characteristics of the disease, measures of disease activity and functional disability, and potential laboratory biomarkers in the prediction of response, defined as the achievement of modified-minimal disease activity (mMDA), to golimumab in PsA patients.

Results

We studied 151 PsA patients starting golimumab because of their active disease. After 6 months, the rate of drug persistence on golimumab was 80%, and mMDA was achieved in 44.3% of patients. Using univariate and multivariate logistic regression models, lower disease activity in PsA score (DAPSA) at baseline (odds ratio [OR] 0.92; 95% confidence interval [CI] 0.89–0.96, p<0.001) was independent predictor of mMDA at 6 months. High sensitivity C-reactive protein value (OR 1.06; 95% CI 1.00–1.13, p=0.026) at baseline also was a predictive factor of mMDA achievement at 6 months in the laboratory-enhanced prediction model. Golimumab was safe and well tolerated.

Conclusion

The identification of factors predictive of response to treatment may help in better understanding the response to golimumab and in identifying PsA patients that are most likely to achieve mMDA following therapy with golimumab.

Key words

psoriatic arthritis, golimumab, modified minimal disease activity, predictors, biomarkers

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Introduction

Psoriatic arthritis (PsA) is a chronic systemic disease characterised by inflammation of the joints and surrounding structures associated with psoriasis. Arthritis of the peripheral and axial joints, inflammation of entheses, dactylitis, onychopathy together with skin involvement is the wide spectrum of PsA manifestations that can impact patients' quality of life (1-3). The introduction of highly effective biologic drugs, particularly the inhibitors of tumour necrosis factor alpha (TNF-α), has changed the therapeutic approach to patients with PsA, and has allowed long-term disease control (4-6). Therefore, the achievement of remission is becoming an ambitious goal in the treatment strategy, but an established definition of clinical remission of PsA is still lacking (7). Alternatively, the lowest level of disease activity, possibly in most domains of PsA, may be a wishful outcome. The GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) project developed a PsA-specific definition of minimal disease activity (MDA), allowing for more specific evaluation of disease activity and desirable disease status (8). The target criteria identified by this study group comprised the evaluation of tender joint count (TJC), swollen joint count (SJC), psoriasis activity and severity index (PASI) or body surface area (BSA) for skin involvement, pain visual analogue scale (VAS), patient global disease activity VAS, health assessment questionnaire (HAQ) disability score and number of tender entheseal points. A post-hoc analysis of the ADEPT (Adalimumab Effectiveness in Psoriatic Arthritis Trial) study (9) demonstrated that the modification of the MDA (modified MDA - mMDA) by replacing PASI ≤1 with physician global assessment (PGA) for psoriasis activity did not modify the results, improving indeed reliability and feasibility in clinical practice. In fact, although used extensively in clinical trials, the PASI is not a sensitive-to-change measure when small skin areas are involved, and it is not often employed in clinical practice (10). Conversely, the PGA for psoriasis activity is a simplified measure reflecting the physician impression on global improvement from baseline and may be appropriate for use in community-based outcomes projects (11).

Although anti-TNF-α therapies have revolutionised the management of PsA, approximately 20–30% of patients fail to respond (12, 13). Furthermore, given the risk of adverse events (AEs) and the considerable costs of biologics, there is a need to identify predictors of response to optimise the treatment (14).

In recent years, several studies using different strategies have been carried out to identify markers that may predict treatment outcome in rheumatoid arthritis (RA) patients and hence help clinicians in decisions on management strategies (15). Based on this background, we have developed a clinical prediction model for the achievement of 6-month mMDA in PsA patients starting golimumab, a fully human monoclonal antibody targeting TNF-α which was approved as monotherapy and/or in combination with methotrexate for the treatment of inflammatory arthritis, including PsA (16). The identification of predictors of response to biologic therapies would decrease the number of non-responding patients and hence may help in optimising medical cost-effectiveness.

Materials and methods

The study population included all patients referred to participating clinics who fulfilled the following criteria: age ≥18 years with PsA as per Classification for Psoriatic Arthritis (CASPAR) criteria; non-responders or insufficient responders to conventional therapies according to physician's judgement; newly prescribed golimumab according to usual clinical practice; naive to anti-TNF-α or other biologic agents prior to golimumab initiation; use of a medically accepted method of contraception in females in childbearing age. Patients with prior or current use of anti-TNF-α or other biologic agents for any disease, or who had already started treatment with golimumab, or patients showing mMDA at screening were excluded from the study. Concomitant treatment with conventional synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs) was allowed.

Patients were followed prospectively and data were collected at baseline (pre-treatment) and after 3 and 6 months (± 4 weeks). Clinical variables were collected as part of standard clinical care. Treatment was chosen at the discretion of the participating investigators according to clinical judgement and local standard of care.

The following parameters were recorded at baseline: demographics (age and gender), physical characteristics (weight and height), smoking history, disease duration, presence of metabolic syndrome and comorbidities. The following disease-related parameters were recorded at baseline and after 3 and 6 months: 68-TJC, 66-SJC, PGA of psoriasis activity (clear or almost clear), patient global assessment of pain, patient global assessment of disease activity, and PGA for psoriasis activity (all on a 100-mm VAS), functional status (HAQ), Leeds Enthesitis Index (LEI), dactylitis score, laboratory tests (haematology, blood chemistry, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] locally measured at sites), disease activity in psoriatic arthritis (DAPSA), medications for PsA and comorbidities. Furthermore, the following laboratory parameters were assayed in a central laboratory following frozen shipments (Quintiles Ltd, The Alba Campus, Rosebank, Livingston, United Kingdom) at baseline and at 6 months: high sensitivity CRP (hs-CRP), matrix metalloproteinase-3 (MMP-3) and C-terminal pro-peptides of type II procollagen (CPII). Standard ELISA was used for the assay of MMP-3 and CPII, and an automated chemistry analyser was used for the hs-CRP assay.

The primary endpoint of the study was the percentage of patients achieving mMDA at 6 months. For the evaluation of psoriasis activity, PASI ≤1 was substituted with PGA "clear" or "almost clear" for adaptation to the mMDA (7). PsA patients were classified as having mMDA if they met at least 5 of these 7 criteria: TJC ≤1, SJC ≤1, clear or almost clear PGA for psoriasis activity, patient pain VAS ≤15, patient global assessment of disease activity VAS ≤20, HAQ total score ≤0.5, LEI ≤1. The secondary endpoints of the study were: proportion of patients achieving mMDA at 3 months; changes from baseline to months 3 and 6 of clinical outcomes (LEI, dactilytis score, HAQ, DAPSA). The HAQ is a self-administered questionnaire assessing the patient's functional ability during the last week (17). The LEI (18) includes an assessment of tenderness in 6 different sites. The tender dactylitis count (range 0–20) is a simple count based on the number of digits thought to have dactylitis. The DAPSA was adapted from the DAREA (disease activity score for reactive arthritis), a score validated for reactive arthritis (19). It was developed from a clinical cohort and validated using clinical trial data (20). It comprises 5 untransformed, unweighted variables, including 2 patient-centred items (patient assessment of disease activity and pain, both on an 11-point numeric rating scale [NRS]), one physician-centred item (66-SJC), one item dependent on patient and physician (68-TJC) and CRP (mg/dl). The composite score is a simple sum of the 5 items. Safety of golimumab was evaluated by collection of adverse events (AEs) during the study. All assessments were performed by a rheumatologist.

The study protocol was approved by the ethics committee of the coordinating centre and by the reference local ethic committees of each participating site. All patients provided written informed consent prior to any study-related procedure was started.

The sample size was estimated based on the primary objective of the cohort study, *i.e.* to develop a clinical prediction model of achievement of 6-month mMDA in PsA patients starting golimumab. To avoid over-fitting, the minimum number of events per variable was set to 10. Given an expected 6-month mMDA achievement rate of 40%, 125 subjects were to be enrolled to develop a prediction model including up to 5 variables. Assuming approximately 10% of lost to follow-up patients, sample rose to 135–140 subjects. Because of the higher clinical relevance of minimising false negative responders, power calculation was performed to evaluate the improvement of the true positive rate from 60 to 70% and improvement of false negative rate from 40 to 15%, setting alpha to 5%. A number of 125 subjects with 50 responders would be sufficient to evaluate the increase in the performance of the model laboratory-enhanced prediction model with a power >80% (estimated in Stata using resize command).

The list of candidate predictors retrieved from the literature was restricted based on the a priori relevance (consistency across studies), distribution, and by combining similar predictors, and were: gender, age, body mass index (BMI), smoking history, time from diagnosis and symptoms duration before diagnosis, presence of comorbidities and polyarthritis, concurrent use of DMARDs and glucocorticoids, CRP, DAPSA score, HAQ total score, VAS patient global assessment of pain, presence of psoriasis/nail psoriasis (where PGA "clear" or "almost clear" meant "no psoriasis"), all at baseline. Missing values in predictors (including items of composite scores) were systematically evaluated and multiple imputation (>10 datasets) was carried out (no imputation of outcome was done).

Predictors of mMDA at 3 and 6 months were individually tested by univariate logistic models and results were presented as odds ratio (OR) and 95% confidence interval (CI). A backward stepwise selection strategy (cut-off: $p<0.10$) was applied to multivariate logistic model to further select relevant variables. Internal validity of the prediction models was tested by bootstrap validation using 500 bootstrap repetitions on a sample with 50% size of the sample included in the model. Further logistic models for the outcome of mMDA at 3 and 6 months were fitted including baseline levels of laboratory parameters dosed in the central laboratory (*i.e.* hs-CRP in place of CRP). The improvement of the performance of the prediction models was evaluated by estimating the integrated discrimination improvement (IDI) index. Predictors of the secondary response outcomes (LEI, dactylitis score, HAQ, DAPSA 0–6 month changes) were explored using linear regression models, as for the primary outcome.

The data analysis was performed using

Table I. Demographic and baseline clinical characteristics.

Gender, n (%)	n=149
Male	80 (53.7%)
Female	69 (46.3%)
Age (years)	n=149
Mean ± SD	49.16 ± 11.25
Median (range)	50.0 (21-75)
Ethnicity, n (%)	n=149
Caucasian	146 (98.0%)
Non-Caucasian	3 (2.0%)
Time from first PsA diagnosis (months)	n=149
Mean ± SD	45.49 ± 70.58
Median (range)	21.47 (0.03-554.47)
Time from onset of PsA symptoms (months)	n=139
Mean ± SD	84.60 ± 95.30
Median (range)	53.43 (2.17-554.47)
CRP (nmol/L)*	n=149
Mean ± SD	136.25 ± 316.56
Median (range)	51.43 (0.00-3047.68)
ESR (mm/h)	n=149
Mean ± SD	23.35 ± 19.633
Median (range)	19.00 (2-120)
68-TJC	n=149
Mean ± SD	11.77 ± 9.52
Median (range)	10.00 (1-55)
66-SJC	n=149
Mean ± SD	4.73 ± 4.69
Median (range)	4.00 (0-22)
Patient assessment of pain VAS (mm)	n=149
Mean ± SD	61.18 ± 24.37
Median (range)	64.00 (3-100)
Patient global assessment of disease activity VAS (mm)	n=149
Mean ± SD	63.25 ± 19.45
Median (range)	65.00 (11-100)
PGA of disease activity VAS (mm)	n=149
Mean ± SD	54.80 ± 19.27
Median (range)	55.00 (10-98)
HAQ (total score)	n=149
Mean ± SD	0.95 ± 0.60
Median (range)	0.88 (0.00-2.75)
LEI (score)	n=149
Mean ± SD	1.91 ± 1.65
Median (range)	2.00 (0-6)
Dactylitis (digit count)	n=149
Mean ± SD	0.60 ± 1.40
Median (range)	0.00 (0-10)
DAPSA (total score)	n=149
Mean ± SD	30.27 ± 14.51
Median (range)	27.20 (7.75-82.35)

n: number of observations.
*Dosed locally at sites.

the SAS System v. 9.4 under Windows 10 PRO operating system, in all enrolled subjects who received at least one dose of golimumab. Continuous variables were summarised using number of patients, mean, standard deviation (SD), median and range. For categorical variables, data were summarised by number and percentage of subjects.

Table II. Summary of the proportion of patients achieving mMDA at 3 and 6 months.

	mMDA at 3 months (n=149)	mMDA at 6 months (n=149)
Tender joint count, n (%)		
>1	77 (51.7%)	62 (41.6%)
≤1	61 (40.9%)	63 (42.3%)
Unknown	11 (7.4%)	24 (16.1%)
Swollen joint count, n (%)		
>1	32 (21.5%)	16 (10.7%)
≤1	106 (71.1%)	109 (73.2%)
Unknown	11 (7.4%)	24 (16.1%)
PGA for psoriatic activity, n (%)		
Clear or almost clear	123 (82.6%)	115 (77.2%)
Other	15 (10.1%)	10 (6.7%)
Unknown	11 (7.4%)	24 (16.1%)
Patient assessment of pain VAS, n (%)		
>15 mm	96 (64.4%)	71 (47.7%)
≤15 mm	42 (28.2%)	54 (36.2%)
Unknown	11 (7.4%)	24 (16.1%)
Patient global assessment of disease activity VAS, n (%)		
>20 mm	100 (67.1%)	69 (46.3%)
≤20 mm	38 (25.5%)	56 (37.6%)
Unknown	11 (7.4%)	24 (16.1%)
HAQ total score, n (%)		
>0.5	65 (43.6%)	48 (32.2%)
≤0.5	73 (49.0%)	77 (51.7%)
Unknown	11 (7.4%)	24 (16.1%)
LEI score, n (%)		
> 1	28 (18.8%)	20 (13.4%)
≤1	110 (73.8%)	105 (70.5%)
Unknown	11 (7.4%)	24 (16.1%)
mMDA achieved, n (%)		
No	84 (56.4%)	59 (39.6%)
Yes	54 (36.2%)	66 (44.3%)
Unknown	11 (7.4%)	24 (16.1%)

n: number of patients.

Results

Overall, 151 patients were enrolled in 23 Rheumatology sites in Italy from May 2015 to May 2016, and 125 (82.8%) completed the 6-month observational period, whereas 26 (17.2%) prematurely discontinued the study because lost to follow-up (n=9), withdrawal of consent (n=3) or other reasons (n=14). Treatment at the end of study was ongoing in 120 patients (79.5% of enrolled). Of the 151 enrolled patients, 2 patients (1.3%) that withdrew consent before starting golimumab were excluded from the analysis set.

Table I shows the demographics and other baseline characteristics of patients. Polyarthritis was reported in 135 patients (90.6%). Hypertension (n=33, 22.1%), thyroid disorder (n=18, 12.1%), liver disorder (n=11, 7.4%) and hypercholesterolaemia (n=11, 7.4%) were the most common comorbidities. At baseline, glucocorticoids were taken by 55 patients (36.9%), non-steroidal anti-inflammatory drugs (NSAIDs) by 59 (39.6%), csDMARDs by 106 (71.1%) (87 of which [58.6%] taking methotrexate).

Table II shows the proportion of patients achieving mMDA at 3 and 6 months. Overall, 66 patients (44.3%) achieved the mMDA at 6 months, and 59 (39.6%) did not. The results were unknown in 24 patients (16.1%). The highest response rates were observed in patients with TJC ≤1, SJC ≤1 and LEI ≤1.

Factors associated to the achievement of mMDA at 6 months are shown in Table III. The backward stepwise multivariate logistic model selected 4 factors independently associated to mMDA at 6 months. Lower DAPSA score at baseline (OR 0.93, 95% CI 0.89-0.96,

Table III. Summary of factors that resulted to be predictive of mMDA at 6 months.

Used model	Parameter	Item considered	Odds ratio	95% CI	*p*-value	n. of observations
Univariate logistic model	Gender	Female	0.32	0.15- 0.67	0.002	125
	Age	Continuous	0.96	0.93-0.99	0.011	125
	DAPSA score at baseline	Continuous	0.93	0.90-0.96	<0.001	125
	HAQ total score at baseline	Continuous	0.29	0.14-0.60	<0.001	125
	Pain VAS at baseline	Continuous	0.98	0.97-0.10	0.030	125
	Comorbidities	Presence	0.33	0.15-0.72	0.006	125
Multivariate logistic model [(1)]	Age	Continuous	0.95	0.91-1.00	0.047	117
	CRP at baseline	Continuous	1.00	1.00-1.00	0.024	
	DAPSA score at baseline	Continuous	0.93	0.89-0.96	<0.001	
	Duration of symptoms at baseline	Continuous	1.01	1.01-1.02	0.026	
Laboratory-enhanced univariate logistic model	hs-CRP at baseline	Continuous	1.07	1.01 to 1.13	0.026	125
Laboratory-enhanced multivariate logistic model [(2)]	Comorbidities	Presence	0.27	0.09 to 0.79	0.018	98
	DAPSA score at baseline	Continuous	0.92	0.89 to 0.96	<0.001	

[(1)]The following factors remained in the model following the backward stepwise selection: age, CRP at baseline, presence of comorbidities, DAPSA score at baseline and duration of symptoms before diagnosis.
[(2)]The following factors remained in the model following the backward stepwise selection: hs-CRP at baseline, presence of comorbidities, DAPSA score at baseline and presence of psoriasis/nail psoriasis at baseline.

p<0.001) was the strongest positive predictor of achievement of mMDA at 6 months; lower age, higher CRP and longer duration of disease also were significantly associated. In the laboratory-enhanced clinical prediction model, presence of comorbidities (OR 0.26, 95% CI 0.09–0.79, *p*=0.018) and lower DAPSA score at baseline (OR 0.92, 95% CI 0.89-0.96, *p*<0.001) in the multivariate logistic model were associated to higher probability to achieve mMDA at 6 months.

At 3 months, 54 patients (36.2%) achieved the mMDA and 84 (56.4%) did not. The results were unknown in 11 patients (7.4%). At 3 months, factors predictive of mMDA based on the multivariate logistic model were lower age, higher CRP value at baseline, lower DAPSA score and HAQ score at baseline, and longer time from diagnosis. In the laboratory-enhanced clinical prediction model, lower age, lower DAPSA score at baseline, and longer time from diagnosis in the multivariate logistic model were indicative of a higher probability to achieve mMDA at 3 months.

Table IV shows the results of changes from baseline to month 3 and 6 of outcome measures. Treatment with golimumab was associated with improvements in all disease and functional parameters measured by patient and physician, and in laboratory markers of disease activity: improvements from baseline were evident just after 3 months of treatment and further increased at 6 months. The assessment of PGA for psoriatic activity showed that, at month 6, the skin assessment was clear in 84 patients (56.4%), almost clear in 31 (20.8%) and mild in 10 (6.7%). None of patients had a mild-to-moderate, moderate, moderate-to-severe, or severe assessment. The result was unknown in 24 patients (16.1%). The results of centralised laboratory parameters (Table V) showed marked decreases from baseline to month 6 in hs-CRP and MMP-3, and no important changes in CPII.

Factors predictive of decrease in HAQ at 6 months in the multivariate linear regression model were age (parameter estimate [PE]=0.0093; *p*=0.013), baseline DAPSA (PE=0.0098; *p*=0.002), and HAQ (PE=-0.6518; *p*<0.001) and presence of psoriasis/nail psoriasis at baseline (PE=-0.1626; *p*=0.049). In the laboratory-enhanced prediction model, age (PE=0.0090; *p*=0.032), baseline DAPSA (PE=0.0071; *p*=0.037), HAQ (PE=-0.6616; *p*<0.001), and MMP-3 (PE=-0.0018; *p*=0.041) were the predictive factors following the backward stepwise selection. Factors predictive of decrease in LEI at 6 months (non-laboratory-enhanced clinical univariate linear regression model) were baseline DAPSA (PE=-0.0266; *p*=0.004), HAQ (PE=-0.5956; *p*=0.014) and patient assessment of pain VAS (PE=-0.0162; *p*=0.004).

Baseline HAQ was the only factor predictive of decrease in dactylitis count at 6 months (PE=0.4758; *p*=0.012), and in the laboratory-enhanced prediction model (PE=0.6807; *p*=0.006). Predictors of decrease in DAPSA score at 6 months in the multivariate linear regression model were gender (PE=4.1751; *p*=0.028), BMI (PE=0.6535; *p*=0.003), baseline DAPSA (PE=-0.5367; *p*<0.001), and baseline VAS pain (PE=-0.1006; *p*=0.020). In the laboratory-enhanced prediction model, gender (PE=4.3610; *p*=0.038), BMI (PE=0.5320; *p*=0.025), time from diagnosis (PE=-0.0292; *p*=0.019), baseline DAPSA (PE=-0.5027; *p*<0.001), and VAS pain (PE=-0.1283; *p*=0.008) were the predictive factors.

AEs were reported in 14 patients (9.4%) and were considered related to golimumab in 12 (8.1%). Leukopenia, erysipelas and alanine aminotransferase increase were the treatment-related AEs observed in 2 patients (1.3%), and the other treatment-related AEs observed in one patient were: thrombocytopenia, bronchitis, genital candidiasis, pharyngotonsillitis, urinary tract infection, aspartate aminotransferase increase, dyspnoea, alopecia, pruritus, psoriasis, pustular psoriasis, erythematous rash and papular rash. Three serious

Table IV. Summary of the results of outcome measures at 3 and 6 months. Data are changes from baseline visit.

	Month 3	Month 6
CRP (nmol/L)*	n=131	n=120
Mean change ± SD	-88.69 ± 291.66	-96.61 ± 308.54
Median change (range)	-26.67 (-2905.77 to 169.53)	-27.62 (-3001.96 to 205.72)
ESR (mm/h)	n=130	n=119
Mean change ± SD	-11.71 ± 17.87	-11.83 ± 17.89
Median change (range)	-6.00 (-114 to 15)	-7.00 (-102 to 11)
68-TJC	n=138	n=125
Mean change ± SD	-6.97 ± 7.29	-7.72 ± 7.75
Median change (range)	-6.00 (-43 to 12)	-6.00 (-41 to 13)
66-SJC	n=138	n=125
Mean change ± SD	-3.33 ± 4.26	-4.09 ± 4.17
Median change (range)	-2.00 (-21 to 6)	-3.00 (-21 to 2)
Patient assessment of pain VAS (mm)	n=138	n=125
Mean change ± SD	-25.50 ± 32.17	-30.59 ± 33.61
Median change (range)	-23.50 (-99 to 54)	-31.00 (-100 to 75)
Patient global assessment of disease activity VAS (mm)	n=138	n=125
Mean change ± SD	-23.39 ± 28.64	-31.38 ± 30.38
Median change (range)	-21.00 (-91 to 47)	-34.00 (-92 to 55)
PGA of disease activity VAS (mm)	n=138	n=125
Mean change ± SD	-31.67 ± 20.14	-38.82 ± 21.93
Median change (range)	-31.00 (-83 to 15)	-40.00 (-84 to 18)
HAQ (total score)	n=138	n=125
Mean change ± SD	-0.34 ± 0.50	-0.41 ± 0.52
Median change (range)	-0.31 (-1.50 to 0.75)	-0.38 (-1.88 to 1.13)
LEI (score)	n=138	n=125
Mean change ± SD	-1.07 ± 1.45	-1.27 ± 1.53
Median change (range)	-1.00 (-6 to 3)	-1.00 (-6 to 3)
Dactylitis (digit count)	n=138	n=125
Mean change ± SD	-0.47 ± 1.13	-0.46 ± 1.12
Median change (range)	0.00 (-6 to 2)	0.00 (-6 to 2)
DAPSA (total score)	n=131	n=120
Mean change ± SD	-16.17 ± 12.14	-19.16 ± 13.04
Median change (range)	-14.32 (-70.75 to 15.00)	-17.12 (-67.50 to 20.19)

n: number of observations. *Dosed locally at sites.

AEs (basal cell carcinoma, methotrexate toxic hepatitis and bilateral cervical lymphadenopathy) were reported in 3 patients (2.0%) and none was fatal or related to golimumab. Six (4.0%) and 5 patients (3.4%) temporarily and permanently discontinued golimumab due to AEs, respectively.

Discussion

The main findings of this study have shown that 44.3% of evaluable biologic-naive patients with active PsA have achieved mMDA after 6 months of treatment with golimumab. Baseline predictors of mMDA at 6 months were lower age, higher CRP, lower DAPSA, and longer disease duration. Lower DAPSA score appeared to be the strongest predictor of response to treatment with golimumab. Furthermore, treatment with golimumab was associated with improvements in secondary endpoints (LEI score, dactylitis digit count, HAQ total score, and DAPSA). Improvements were already evident after 3 months of treatment and were sustained up to 6 months. At 6 months, approximately 80% of patients were still receiving golimumab. The high persistency to treatment with golimumab was consistent with data at 6 months from real-world evidence of use of golimumab in immune-mediated rheumatic diseases, which showed that golimumab may have higher persistency than other TNF-α inhibitors (21). A recent observational cohort study has shown that golimumab has high retention rate in real-life settings and that patients attaining an early clinical response had the highest probability to continue golimumab over 2 years (22). High retention rates with golimumab (23, 24) and other anti-TNF-α therapies (25) have been reported in the management of arthritic diseases.

The factors predicting response to therapy identified in this study are partially consistent with those reported in prior studies. In a previous study with adalimumab, lower impairment of physical function, greater pain, male gender and no systemic glucocorticoids were factors that increased the chance of achieving a good EULAR response (26). In the Swedish Early Psoriatic Arthritis (SwePsA) Register (27), the most important predictors of MDA at the 5-year follow-up were short lag between onset of symptoms and diagnosis, preserved function and male gender. Furthermore, PsA naïve-biologic patients from the British Society for Rheumatology Biologics Register, a better 5-year persistence was associated with male gender, use of etanercept or adalimumab

Table V. Summary of the results of centralised laboratory parameters.

	Baseline	Month 6	Change from baseline to month 6
hs-CRP (mg/L)	n=146	n=116	n=116
Mean ± SD	7.46 ± 14.95	2.59 ± 3.14	-4.68 ± 15.42
Median (range)	2.77 (0.21 to 117.42)	1.38 (0.18 to 22.54)	-0.81 (-109.72 to 20.78)
MMP-3 (μg/L)	n=143	n=105	n=104
Mean ± SD	41.16 ± 45.89	22.56 ± 20.68	-21.01 ± 42.03
Median (range)	26.71 (4.24 to 298.92)	16.42 (1.34 to 125.21)	-7.41 (-279.85 to 36.46)
CPII (ng/ml)	n=121	n=95	n=91
Mean ± SD	2289.0 ± 1102.7	2512.5 ± 1067.6	88.3 ± 661.1
Median (range)	2133.8 (100.0 to 4000.0)	2438.4 (633.8 to 4000.0)	0.0 (-2098.8 to 2121.2)

rather than infliximab and absence of comorbidities (28). In an Italian cohort study in patients with PsA receiving anti-TNF-α, age and Bath ankylosing spondylitis functional index (BASFI) inversely predicted, whereas CRP directly predicted, achievement of MDA after 3 months of treatment (29).

Previous studies evaluated the role of potential biomarkers in clinical response in PsA patients. Baseline levels of MMP-3 and their reduction over time, and the increase in serum cartilage oligomeric matrix protein (COMP) were independently associated with response to anti-TNF-α therapy (30).

In a recent prospective observational study adopting a similar definition of MDA, male sex, high CRP, high ESR and low HAQ were found to be predictor for MDA in patients treated with TNF-α blockers (31). Yet, lower baseline HAQ and lower TJC-28 were identified as significant prognostic factors of MDA achievement (in 43.5% of patients at 6 months) in a real-world survey in patients with PsA receiving infliximab and golimumab (32).

Our study has some important limitations in terms of generalisability of the results. Due to the observational nature of the study, no control groups were used and therefore a prediction model developed in a population of PsA treated with golimumab is not directly applicable to other drugs. Furthermore, the selection of PsA patients in a single-country study might not reflect the general population treated with golimumab in terms of genetic background, disease duration, previous exposure to non-biologic/biologic DMARDs. It should also be considered that previous studies that have investigated the prediction role of different factors in response to treatment in PsA patients may differ from this study in terms of drug under study, criteria for eligibility of participants, selection of pre-defined factors, methods of assessments and duration of exposure to drug. In this study, the standard candidate predictors retrieved from the literature (30, 33, 34) were combined in a first prediction model and then soluble parameters (hs-CRP, MMP-3, CPII) for the improvement of the performance of the clinical prediction model were evaluated and added in the laboratory-enhanced clinical prediction model. The use of the biomarker-enhanced model increased the spectrum of predictive factors for achievement of mMDA at 6 months with higher hs-CRP value at baseline, absence of comorbidities and lower DAPSA score at baseline. Notably, the DAPSA score at baseline was the factor that was associated with mMDA in most of tests. This is not surprising as DAPSA is a validated composite measure that takes into consideration subjective and objective items, including the joint state and CRP (20), and hence better reflects the PsA activity than other single parameters. Data from trials with TNF-α inhibitors have shown that higher DAPSA scores are significantly and independently associated with probability of structural damage progression in PsA, thus further supporting the use of the PsA-specific DAPSA score as endpoints in clinical trials or as targets in common clinical practice (35).

In conclusion, this observational study has shown that lower DAPSA score at baseline was the strongest predictors of mMDA at 6 months in naïve-biologic PsA patients on treatment with golimumab. Due to the heterogeneity in methods for assessment of response to treatment available in literature, measures used for the definition of mMDA and predictive factors of treatment response identified in this study, our results should undergo an external validation in order to be eventually applicable in the selection of PsA patients that are most likely to respond to golimumab.

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References

1. GLADMAN D, ANTONI C, MEASE P, CLEGG DO, NASH P: Psoriatic arthritis: epidemiology, clinical features, course and outcome. *Ann Rheum Dis* 2005; 64: ii14-ii17.
2. TERENZI R, MONTI S, TESEI G, CARLI L: One year in review 2017: spondyloarthritis. *Clin Exp Rheumatol* 2018; 36: 1-14.
3. RITCHILIN CT, KAVANAUGH A, GLADMANN DD AND GROUP FOR RESEARCH AND ASSESSMENT OF PSORIASIS AND PSORIATIC ARTHRITIS (GRAPPA): Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 2009; 68: 1387-94.
4. ANTONI CE, KAVANAUGH A, KIRKHAM B *et al*.: Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum* 2005; 52: 1227-36.
5. KAVANAUGH A, MCINNES IB, MEASE PJ, KRUEGER GG, GLADMAN DD, VAN DER HEIJDE D: 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 GOREVEAL study. *Ann Rheum Dis* 2013; 72: 1777-85.
6. MEASE PJ: Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomized placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; 73: 48-55.
7. LUBRANO E, MESINA F, CAPORALI R: Clinical remission in rheumatoid arthritis and psoriatic arthritis. *Clin Exp Rheumatol* 2018; 36: 900-10.
8. COATES LC, FRANSEN J, HELLIWELL PS: Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010; 69: 48-53.
9. MEASE PJ, HECKAMAN M, KARY S, KUPPER H: Application and modification of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: subanalyses of ADEPT. *J Rheumatol* 2013; 40: 647-52.
10. FELDMAN SR, KRUEGER GG: Psoriasis assessment tools in clinical trials. *Ann Rheum Dis* 2005; 64 (Suppl. 2): ii65-8.
11. ROBINSON A, KARDOS M, KIMBALL AB: Physician global assessment (PGA) and Psoriasis Area and Severity Index (PASI): Why do both? A systematic analysis of ran-

domized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol* 2012; 66: 369-75.
12. MEASE PJ: Psoriatic arthritis: Update on pathophysiology, assessment and management. *Ann Rheum Dis* 2011; 70 Suppl. 1: i77-84.
13. IANNONE F, LOPRIORE S, BUCCI R *et al*.: 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.
14. VILLANOVA F, DI MEGLIO P, O NESTLE F: Biomarkers in psoriasis and psoriatic arthritis. *Ann Rheum Dis* 2013; 72: 104-10.
15. CUPPEN BV, WELSING PM, SPRENGERS JJ *et al*.: Personalized biological treatment for rheumatoid arthritis: a systematic review with a focus on clinical applicability. *Rheumatology* (Oxford) 2016; 55: 826-39.
16. FRAMPTON JE: Golimumab: a review in inflammatory arthritis. *BioDrugs* 2017; 31: 263-74.
17. HUSTED JA, GLADMAN DD, LONG JA, FAREWELL VT: A modified version of the health assessment questionnaire (HAQ) for psoriatic arthritis. *Clin Exp Rheumatol* 1995; 13: 439-43.
18. HEALY PJ, HELLIWELL PS: Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum* 2008; 59: 686-91.
19. EBERL G, STUDNICKA-BENKE A, HITZELHAMMER H, GSCHNAIT F, SMOLEN JS: Development of a disease activity index for the assessment of reactive arthritis (DAREA). *Rheumatology* 2000; 39: 148–55.
20. NELL-DUXNEUNER VP, STAMM TA, MACHOLD KP, PFLUGBEIL S, ALETAHA D, SMOLEN JS: Evaluation of the appropriateness of composite disease activity measures for assessment of psoriatic arthritis. *Ann Rheum Dis* 2010; 69: 546-9.
21. SVEDBOM A, STORCK C, KACHROO S, GOVONI M, KHALIFA A: Persistence with golimumab in immune-mediated rheumatic diseases: a systematic review of real-world evidence in rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis. *Patient Prefer Adherence* 2017; 11: 719-29.
22. IANNONE F, SANTO L, ANELLI MG *et al*.: Golimumab in real-life settings: 2 Years drug survival and predictors of clinical outcomes in rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. *Semin Arthritis Rheum* 2017; 47: 108-14.
23. THOMAS K, FLOURI I, REPA A *et al*.: High 3-year golimumab survival in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: real world data from 328 patients. *Clin Exp Rheumatol* 2018; 36: 254-62.
24. MANARA M, CAPORALI R, FAVALLI EG *et al*.: Two-year retention rate of golimumab in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: data from the LORHEN registry. *Clin Exp Rheumatol* 2017; 35: 804-9.
25. SOUBRIER M, PEREIRA B, FRAYSSAC T *et al*.: Psoriatic arthritis treated by anti-TNFs: a monocentric trial of 102 cases in Auvergne, France. *Clin Exp Rheumatol* 2016; 34: 1059-64.
26. VAN DEN BOSCH F, MANGER B, GOUPILLE P *et al*.: Effectiveness of adalimumab in treating patients with active PsA and predictors of good clinical responses for arthritis, skin and nail lesions. *Ann Rheum Dis* 2010; 69: 334-99.
27. THEANDER L, HUSMARK T, ALENIUS GM *et al*.: Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). *Ann Rheum Dis* 2014; 73: 407-13.
28. FAGERLI KM, KEARSLEY-FLEET L, WATSON KD *et al*.: Long-term persistence of TNF-inhibitor treatment in patients with psoriatic arthritis. Data from the British Society for Rheumatology Biologics Register. *RMD Open* 2018; 4: e000596.
29. IERVOLINO S, DI MINNO MN, PELUSO R, LOFRANO M, RUSSOLILLO A, DI MINNO G: Predictors of early minimal disease activity in patients with psoriatic arthritis treated with tumor necrosis factor-a blockers. *J Rheumatol* 2012; 39: 568-73.
30. CHANDRAN V, SHEN H, POLLOCK RA *et al*.: Soluble biomarkers associated with response to treatment with tumor necrosis factor inhibitors in psoriatic arthritis. *J Rheumatol* 2013; 40: 866-71.
31. PERROTTA FM, MARCHESONI A, LUBRANO E: Minimal disease activity and remission in psoriatic arthritis patients treated with anti-TNF-α drugs. *J Rheumatol* 2016; 43: 350-5.
32. RAHMAN P, ZUMMER M, BESSETTE L *et al*.: Real-world validation of the minimal disease activity index in psoriatic arthritis: an analysis from a prospective, observational, biological treatment registry. *BMJ Open* 2017; 7: e016619.
33. WAGNER L, VISVANATHAN S, ELASHOFF M *et al*.: Markers of inflammation and bone remodeling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. *Ann Rheum Dis* 2013; 72: 83-8.
34. FITZGERALD O, MEASE P: Biomarkers: Project Update from the GRAPPA 2012 Annual Meeting. *J Rheumatol* 2013; 40: 1453-4.
35. ALETAHA D, ALASTI F, SMOLEN JS: Disease activity states of the DAPSA, a psoriatic arthritis specific instrument, are valid against functional status and structural progression. *Ann Rheum Dis* 2017; 76: 418-21.