Predictors of response to TNF blockers in patients with polyarticular psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease with a broad clinical spectrum. PsA can affect the axial skeleton, peripheral joints, entheses, synovial sheaths of tendons, skin, nails and extra-articular organs. Tumour necrosis factor alpha blockers (TNF blockers) were a breakthrough development in the treatment of PsA. Identifying predictors of response to biological therapies in patients with PsA is of utmost importance, especially in view of the costs and potential side effects of these agents. The aims of the present study were to determine baseline predictive factors of response to biological therapies, at 3 and 6 months, in PsA patients with polyarticular involvement (with or without axial involvement). Data were collected from the Rheumatic Diseases Portuguese Register (Reuma.pt). Eligible patients had to be anti-TNF-naive at baseline and to have at least 3 months of follow-up after the beginning of TNF blocker therapy. Only patients with information on at least one of the response measures (at 3 or 6 months of follow-up) were included in the analysis. Univariable logistic regression analysis of potential baseline predictors of European League Against Rheumatism (EULAR) good clinical response, EULAR good/moderate response, 28-joint Disease Activity Score with three variables including the erythrocyte sedimentation rate (DAS28-3V-ESR) remission and Health Assessment Questionnaire (HAQ) response were performed. Multivariable logistic regression using a forward selection procedure was used until the best-fit model was obtained, taking confounding effects into account. A total of 180 patients were eligible for the study (mean age 52 years, 54% women). In multivariable analysis at 3 months, females were less likely to attain a good EULAR response [OR=0.082 (95% CI=0.024, 0.278)], a DAS28-3V-ESR remission [OR=0.083 (95% CI=0.017, 0.416)], a moderate or good EULAR response [OR=0.091 (95% CI=0.011, 0.091)] and a HAQ response [OR=0.074 (95% CI=0.009, 0.608)]. At 6 months, female gender was also less likely to achieve a good EULAR response [OR=0.060 (95% CI=0.011, 0.325)], DAS28-3V-ESR remission [OR=0.060 (95% CI=0.012, 0.297)], and a HAQ response [OR=0.138 (95% CI= 0.029, 0.654)]. In this study we found that gender was the most consistent predictor of response to TNF blocker therapy in patients with polyarticular PsA, with females having a lower probability of response compared to males. These findings suggest that gender-related biochemical, hormonal and psychological factors could play an important role in the response to TNF blocker therapy in PsA.

Keywords: Treatment response; TNF blockers; Psoriatic arthritis;

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease characterized by the involvement of peripheral and axial joints, entheses, skin and nails. Tu-

mour necrosis factor (TNF) blockers (adalimumab, etanercept, golimumab, infliximab and certolizumab) were a breakthrough development in the treatment of PsA. These agents have been found, in randomized controlled clinical trials, to effectively improve several manifestations of the disease, including peripheral arthritis, psoriasis, enthesitis and dactylitis, while also preventing radiographic damage[1-7].

According to the Portuguese recommendations for the use of biological therapies in patients with psoriatic arthritis[8], patients should be considered candidates to biological therapy when 5 or more swollen joints (of 66 joint count) are present, on two separate occasions, at least 1 month apart, after failure of conventional therapies. This is defined as an absence of response to treatment with at least one conventional synthetic disease modifying anti-rheumatic drug (csDMARD) (methotrexate or leflunomide), for at least 3 months on a standard (full) target dose, unless there is intolerance, toxicity or contraindication. In the absence of poor prognostic factors, a second csDMARD (methotrexate, sulfasalazine, leflunomide, cyclosporine) or an association of csDMARDs can be considered, with reassessment after 3 additional months of therapy.

The identification of predictors of response could help clinicians to make evidence-based decisions to maximize the benefits of treatment, by targeting subsets of patients most likely to respond, at the early stages of the decision process. This would also improve the cost/benefit and benefit/risk ratios in patients selected to start TNF blocker therapy.

Most studies that evaluated predictors of response to TNF blockers are based on national registries of rheumatic patients. These studies suggested several predictive factors of a better response, including younger age, male gender, number of swollen joints, elevated C-reactive protein (CRP) levels and no use of corticosteroids. Of interest, no significant difference in efficacy has been found between the different anti-TNF therapies[9]. Despite these contributions, predicting response to treatment to biologic DMARDs (bDMARDs) and to other DMARDs is still an important subject of debate and research as highlighted in the recently published European League Against Rheumatism (EULAR) recommendations for the management of PsA[10].

The aim of the present study was to determine baseline predictive factors of response to biological therapies, at 3 and 6 months, in PsA patients with polyarticular involvement (with or without axial involvement).

METHODS

POPULATION

Data were collected from the Rheumatic Diseases Portuguese Register (Reuma.pt), which is a nation-wide prospective longitudinal cohort, initiated in 2006[11,12]. The Portuguese Data Protection Authority and local ethics committees approved this registry and patients gave formal written informed consent to participate in Reuma.pt.

We included all registered patients with the diagnosis of PsA, according to the treating rheumatologist, starting the first TNF blocker agent, and with at least 3 months of follow-up. Patients with oligoarticular or mutilans forms of PsA were excluded. Only patients with information on at least one of the response measures, both at baseline and at 3 or 6 months of follow-up, were included in the analyses.

RESPONSE MEASURES

The primary response outcome was a good EULAR clinical response [improvement in 28-joint Disease Activity Score (DAS28) from baseline >1.2 and DAS28 at endpoint ≤3.2][13]. The validity of the DAS/DAS28 in patients with polyarticular PsA has been consistently shown[14]. The secondary response measures were: EULAR moderate/good response, DAS28 remission (DAS28<2.6) and HAQ response [defined as the achievement of a HAQ ≤0.5 and/or a decrease in the HAQ ≥0.22 (proposed as being the minimal clinically important difference in the HAQ score)][15]. Regarding the DAS28 definition, we used the definition with 3 variables including the erythrocyte sedimentation rate (DAS28-3V-ESR).

DATA COLLECTION

Information on sociodemographic data [age, gender, educational level, current smoking status, current alcohol use, body mass index (BMI)] and clinical data [disease duration since first symptoms, HLA-B27 status, PsA subtype, rheumatoid factor (RF), antibodies anti-cyclic citrullinated peptides (ACPA), presence of extra-articular manifestations, tender and swollen joints (28-count), erythrocyte sedimentation rate (ESR), CRP, patient global assessment (PGA) Visual Analogic Scale (VAS) treatment with methotrexate (MTX), and the TNF blocker used (infliximab, adalimumab, etanercept or golimumab)] were collected at baseline. In the data collected, there were no patients receiving certolizumab as first TNF blocker. Data on

physical function (HAQ) and DAS28-3V-ESR was collected at 3 time points: 0, 3 and 6 months.

STATISTICAL ANALYSIS

Age, female gender, disease duration since diagnosis, smoking status, alcohol use, educational level, BMI, presence of extra-articular manifestations, baseline disease activity measures (tender and swollen joints (28--joint count), ESR and CRP, DAS28-3V-ESR, PGA (VAS scale), treatment with MTX and physical function (HAQ) were analyzed as baseline predictors in univariable logistic regression analysis, using EULAR good clinical response, EULAR good/moderate response, DAS28-3V-ESR remission and HAQ response at 3 months and at 6 months as the dependent variables. Variables with a p-value <0.05 were re-tested in multivariable models. A manual forward selection procedure was performed until the best-fit model was obtained, taking confounding variables into account. Analyses were performed with IBM SPSS Statistics (version 20.0).

RESULTS

PATIENT CHARACTERISTICS

A total of 433 patients registered in Reuma.pt satisfied the eligibility criteria: anti-TNF-naïve, polyarticular PsA and at least 3 months of follow-up. However, after excluding patients without information on at least one of the response measures, at 3 or 6 months of follow-up, a total of 180 patients were available for analysis. There were no clinical or demographic differences between the 180 patients included in the analysis and the 253 patients excluded because of missing response criteria at follow-up (data not shown), except in the number of swollen joints (6.20±4.19 in the included dataset and 4.54±4.54 in the excluded dataset, p-value 0.03) and in the prevalence of HLA-B27 (16.8% in the included dataset and 22.2% in the excluded dataset, p-value 0.003).

The demographic characteristics of the study population, baseline disease activity measures, TNF blocker used and response measures at 3 and 6 months, are presented in Table I.

RESPONSE MEASURES

A good EULAR response was observed in 44.2% and 57.8% of the patients, at 3 months and 6 months, respectively. DAS28-3V-ESR remission was achieved by 31.8% of patients, at 3 months and 49.2%, at 6 months. At 3 months, 83.7% of patients presented a moderate or good EULAR response, which slightly increased to 86.7%, at 6 months. HAQ response was achieved 78.5% and 82.8% of patients, at 3 and 6 months, respectively (Table I).

UNIVARIABLE ANALYSIS

At 3 months, a good EULAR response was more probable in males and in patients with longer disease duration, at the start of the first biologic agent (Table II). DAS28-3V-ESR remission was associated with gender, swollen and tender joints counts, PGA, ESR, DAS28--3V-ESR and HAQ, at baseline (Table III). Moderate/good EULAR response was associated with gender, BMI and HAQ score at baseline (Table IV). The HAQ response was associated with female gender (Table V).

At 6 months, a good EULAR response was associated with current alcohol use and inversely associated with female gender, BMI, tender joints count and PGA (Table II). DAS28-3V-ESR remission was negatively associated with female gender, age, swollen and tender joints counts, CRP, ESR, DAS28-3V-ESR and HAQ at baseline (Table III). Moderate/good EULAR response was associated with MTX use and swollen joint count (Table IV). The HAQ response was associated with female gender (Table V).

MULTIVARIABLE ANALYSIS

In multivariable analysis at 3 months, females were less likely to attain a good EULAR response and this response was also positively associated with increasing disease duration (Table II). DAS28-3V-ESR remission was also less probable in females and it was negatively associated with higher ESR at baseline (Table III). A moderate or good EULAR response and a HAQ response were also less probable in females (Table IV and V).

At 6 months, a good EULAR response was inversely associated with both female gender and higher tender joint count at baseline (Table II). DAS28-3V-ESR remission was less probable in females and it was negatively associated with higher DAS28-3V-ESR at baseline (Table III). A moderate or good EULAR response was only positively associated with methotrexate intake (Table IV). HAQ response was also less probable in females (Table V).

DISCUSSION

Our results identified female gender as a consistent pre-

TABLE I. BASELINE DEMOGRAPHIC, CLINICAL CHARACTERISTICS OF THE STUDY POPULATION AND RESPONSE MEASURES AT 3 AND 6 MONTHS

	Total	
Demographic variables		
Female, n (%)	180	98 (54.4)
Age, mean (S.D.), years	180	52.3 (12.1)
Educational level, mean (S.D.), years	114	8.3 (4.8)
No smoking, n (%)	130	93 (71.5)
No alcohol use, n (%)	125	89 (71.2)
BMI, mean (S.D.)	62	27.6 (5.4)
Disease characteristics		
Presence of HLA-B27, n (%)	61	9 (14.8)
Presence of rheumatoid factor, n (%)	71	3 (4.2)
Presence of anti-CCP, n (%)	50	1 (2.0)
Extra-articular manifestations, n (%)*	180	61 (33.9)
Methotrexate use, n (%)	152	102 (67.1)
Disease duration, mean (S.D.) years	153	11.9 (9.9)
Disease activity at baseline		
Swollen joints (28-count), mean (S.D.)	123	6.2 (4.2)
Tender joints (28-count), mean (S.D.)	123	9.3 (6.7)
PGA (VAS-scale), mean (S.D.)	126	64.4 (22.2)
ESR mm/h, mean (S.D.)	137	37.3 (28.4)
CRP mg/dl, mean (S.D)	130	2.8 (4.8)
DAS28-3V-ESR, mean (S.D.)	119	5.1 (1.3)
HAQ, mean (S.D.)	104	1.2 (0.7)
First TNF inhibitor, n (%)	180	
Infliximab		27 (15.0)
Etanercept		81 (45.0)
Adalimumab		45 (25.0)
Golimumab		27 (15.0)
Response measures at 3 months, n (%)		
Good EULAR response	86	38 (44.2)
DAS28 remission	107	34 (31.8)
Moderate or good EULAR response	86	72 (83.7)
HAQ response	65	51 (78.5)
Response measures at 6 months, nº (%)		
Good EULAR response	90	52 (57.8)
DAS28 remission	130	64 (49.2)
Moderate or good EULAR response	90	78 (86.7)
HAQ response	87	72 (82.8)

n – Number; S.D. – Standard deviation; VAS-scale – Visual Analogic Scale; ESR – Erythrocyte Sedimentation Rate; CRP – C Reactive Protein; DAS28-3V-ESR – Disease Activity Score 28, 3-variables; HAQ – Health Assessment Questionnaire; TNF – Tumour Necrosis Factor; EULAR – European League Against Rheumatism. *Extra-articular manifestations including anterior uveitis, psoriasis, Crohn disease, ulcerative colitis, unspecified colitis, aortitis, enthesitis, dactylitis, atrioventricular block, pericarditis, myocarditis, pulmonary fibrosis, IgA nephropathy, secondary amyloidosis, cauda equine syndrome and other manifestations.

dictor of worse response to the first TNF blocker, in PsA patients with polyarticular disease. Other less robust predictors of good response were longer disease duration until the first biologic, concomitant therapy

TABLE II. BASELINE PREDICTIVE FACTORS OF GOOD EULAR RESPONSE AT 3 AND 6 MONTHS USING UNIVARIABLE AND MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS

	Good EULAR response at 3 months		Good EULAR response at 6 months	
	Univariable logistic regression OR (CI 95%), p-value (n=51 to 86)	Multivariable logistic regression OR (CI 95%), p-value (n=75)	Univariable logistic regression OR (CI 95%), p-value (n=55 to 90)	Multivariable logistic regression OR (CI 95%), p-value (n=42)
Gender (female)	0.154 (0.059,0.401), **p<0.001**	0.082 (0.024,0.278), p<0.001	0.091 (0.032,0.259), **p<0.001**	0.060 (0.011,0.325), p=0.001
Age	1.006 (0.972,1.041), p=0.739		0.985 (0.952,1.019), p=0.381	
Disease duration until first biologic	1.061 (1.009,1.116), **p=0.020**	1.091 (1.026,1.159), p=0.005	0.993 (0.948,1.040), p=0.780	
Educational level (years)	1.015 (0.906,1.137), p=0.797		1.101 (0.971,1.248), p=0.133	
Body mass index (kg/m^2)	0.974 (0.877,1.083), p=0.633		0.875 (0.773,0.990), **p=0.034**	#
Current smoking	0.640 (0.145,2.815), p=0.555		2.500 (0.463,13.495), p=0.287	
Current alcohol use	1.450 (0.440,4.778), p=0.541		5.280 (1.058,26.346), **p=0.042**	2.208 (0.309,15.777), p=0.430
Extra-articular manifestations	0.794 (0.327,1.924), p=0.609		1.750 (0.702,4.360), p=0.230	
Methotrexate use	1.400 (0.547,3.580), p=0.482		1.733 (0.684,4.394), p=0.246	
Swollen joints (28-count)	0.929 (0.830,1.039), p=0.199		0.927 (0.829,1.036), p=0.182	
Tender joints (28-count)	0.960 (0.899,1.026), p=0.229		0.894 (0.830,0.963), **p=0.003**	0.892 (0.801,0.992), p=0.036
PGA (VAS-scale)	0.988 (0.965,1.011), p=0.291		0.977 (0.955,1.000), **p=0.048**	#
CRP (mg/dl)	0.982 (0.902,1.070), p=0.684		0.871 (0.722,1.052), p=0.151	
ESR (mm/h)	0.984 (0.968,1.000), p=0.055		0.988 (0.974,1.002), p=0.105	
DAS28-3V-ESR	0.789 (0.555,1.122), p=0.187		0.701 (0.490,1.004), p=0.052	
HAQ	0.451 (0.191,1.064), p=0.069		0.534 (0.243,1.173), p=0.118	

VAS-scale – Visual Analogic Scale; CRP – C Reactive Protein; DAS28-3V-ESR - Disease Activity Score 28, 3-variables; ESR – Erythrocyte Sedimentation Rate; HAQ – Health Assessment Questionnaire; EULAR - European League Against Rheumatism; OR – Odds Ratio; # – not selected during multivariable logistic regression analysis.

with MTX and lower disease activity at baseline, as indicated by lower ESR, TJC and DAS28 3V-ESR.

The two most common outcomes used to assess predictors of effectiveness of TNF blocker therapy in previous studies were: 1) response, defined by the achievement of remission or low disease activity status, and 2) toxicity and efficacy, as assessed by survival on the medication.(9) We aimed to evaluate predictors of res-

TABLE III. BASELINE PREDICTIVE FACTORS OF DAS28 REMISSION AT 3 AND 6 MONTHS USING UNIVARIABLE AND MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS

	DAS28 remission at 3 months		DAS28 remission at 6 months	
	Univariable logistic regression OR (CI 95%), p-value (n=62 to 107)	**Multivariable logistic regression OR (CI 95%), p-value (n=58)**	**Univariable logistic regression OR (CI 95%), p-value (n=74 to 130)**	**Multivariable logistic regression OR (CI 95%), p-value (n=63)**
Gender (female)	0.093 (0.036,0.241), **p<0.001**	0.083 (0.017,0.416), p=0.002	0.115 (0.052,0.254), **p<0.001**	0.060 (0.012,0.297), p=0.001
Age	0.971 (0.939,1.005), p=0.091		0.959 (0.929,0.989), **p=0.008**	#
Disease duration until first biologic	1.012 (0.968,1.058), p=0.590		0.978 (0.941,1.016), p=0.256	
Educational level (years)	1.056 (0.953,1.170), p=0.300		1.033 (0.942,1.133), p=0.492	
Body mass index (kg/m^2)	0.880 (0.771,1.004), p=0.056		0.934 (0.847,1.030), p=0.171	
Current smoking	0.436 (0.088,2.161), p=0.310		1.000 (0.297,3.365), p=1.000	
Current alcohol use	1.765 (0.545,5.709), p=0.343		1.810 (0.629,5.203), p=0.271	
Extra-articular manifestations	1.047 (0.446,2.459), p=0.916		1.290 (0.620,2.684), p=0.495	
Methotrexate use	0.868 (0.353,2.136), p=0.758		1.423 (0.632,3.206), p=0.395	
Swollen joints (28-count)	0.828 (0.719,0.952), **p=0.008**	#	0.830 (0.730,0.944), **p=0.005**	#
Tender joints (28-count)	0.843 (0.762,0.933), **p=0.001**	#	0.874 (0.805,0.948), **p=0.001**	1.060 (0.879,1.277), p=0.542
PGA (VAS-scale)	0.972 (0.950,0.995), **p=0.016**	#	0.990 (0.971,1.010), p=0.332	
CRP (mg/dl)	0.838 (0.668,1.051), p=0.127		0.758 (0.607,0.946), **p=0.014**	0.959 (0.713,1.291), p=0.784
ESR (mm/h)	0.938 (0.908,0.969), **p<0.001**	0.935 (0.891,0.982), p=0.007	0.967 (0.949,0.985), **p<0.001**	#
DAS28-3V-ESR	0.297 (0.167,0.527), **p<0.001**	#	0.401 (0.521,0.640), **p<0.001**	0.344 (0.133,0.893), p=0.028
HAQ	0.119 (0.400,0.360), **p<0.001**	0.613 (0.140,2.694), p=0.517	0.388 (0.183,0.821), **p=0.013**	2.401 (0.585,9.856), p=0.224

VAS-scale – Visual Analogic Scale; CRP – C Reactive Protein; DAS28-3V-ESR - Disease Activity Score 28, 3-variables; ESR – Erythrocyte Sedimentation Rate; HAQ – Health Assessment Questionnaire; EULAR - European League Against Rheumatism; OR – Odds Ratio;
– not selected during multivariable logistic regression analysis

ponse, using multiple definitions, namely the EULAR response and DAS28-3V-ESR remission criteria, both previously validated in PsA. HAQ response was also analyzed, as this measure of disability has also been validated for patients with PsA[16].

Female gender was a consistent predictive factor of poor response to TNF blockers, as found by Glintborg et al., who analyzed results from 764 patients with PsA receiving TNF blocker therapy, from the nationwide Danish DANBIO registry[17]. In a multiple logistic re-

TABLE IV. BASELINE PREDICTIVE FACTORS OF MODERATE OR GOOD EULAR RESPONSE AT 3 AND 6 MONTHS USING UNIVARIABLE AND MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS

	Moderate or good EULAR response at 3 months		Moderate or good EULAR response at 6 months	
	Univariable logistic regression OR (CI 95%), p-value (n = 51 to 86)	Multivariable logistic regression OR (CI 95%), p-value (n = 38)	Univariable logistic regression OR (CI 95%), p-value (n = 55 to 90)	Multivariable logistic regression OR (CI 95%), p-value (n = 90)
Gender (female)	0.091 (0.011,0.091), **p=0.024**	0.091 (0.011,0.091), p=0.024	0.351 (0.088,1.395), p=0.137	
Age	1.010 (0.966,1.057), p=0.656		1.014 (0.968,1.063), p=0.548	
Disease duration until first biologic	1.006 (0.946,1.070), p=0.851		1.002 (0.936,1.074), p=0.947	
Educational level (years)	1.012 (0.869,1.178), p=0.878		0.915 (0.760,1.102), p=0.349	
Body mass index (kg/m^2)	0.874 (0.765,0.998), **p=0.046**	#	0.934 (0.803,1.085), p=0.371	
Current smoking	0.375 (0.079,1.781), p=0.217		0.549 (0.053,5.639), p=0.614	
Current alcohol use	1.350 (0.256,7.117), p=0.723		1.067 (0.109,10.449), p=0.956	
Extra-articular manifestations	0.754 (0.236,2.410), p=0.633		1.588 (0.397,6.360), p=0.513	
Methotrexate use	1.349 (0.404,4.504), p=0.626		4.667 (1.320,16.497), **p=0.017**	4.667 (1.320,16.497), p=0.017
Swollen joints (28-count)	1.160 (0.968,1.390), p=0.109		1.263 (1.006,1.585), **p=0.045**	#
Tender joints (28-count)	1.009 (0.925,1.100), p=0.847		0.971 (0.887,1.064), p=0.529	
PGA (VAS-scale)	0.972 (0.940,1.004), p=0.090		1.000 (0.971,1.030), p=0.992	
CRP (mg/dl)	1.074 (0.872,1.323), p=0.503		0.995 (0.893,1.108), p=0.924	
ESR (mm/h)	0.990 (0.972,1.007), p=0.251		0.990 (0.972,1.008), p=0.272	
DAS28-3V-ESR	1.080 (0.982,1.712), p=0.742		1.102 (0.679,1.789), p=0.693	
HAQ	0.253 (0.070,0.919), **p=0.037**	#	2.395 (0.739,7.761), p=0.145	

VAS-scale – Visual Analogic Scale; CRP – C Reactive Protein; DAS28-3V-ESR - Disease Activity Score 28, 3-variables; ESR – Erythrocyte Sedimentation Rate; HAQ – Health Assessment Questionnaire; EULAR – European League Against Rheumatism; OR – Odds Ratio; # – not selected during multivariable logistic regression analysis.

gression analysis using EULAR good response as the dependent variable, female gender was associated with a less probable EULAR good clinical response. Saad A. et al. included 596 PsA patients of the British Society for Rheumatology Biologics Register (BSRBR) and found that, for the EULAR response at 6 months, both univariable and multivariable analyses suggested that being female resulted in lower response rates (OR 0.51,

TABLE V. BASELINE PREDICTIVE FACTORS OF HAQ RESPONSE AT 3 AND 6 MONTHS USING UNIVARIABLE AND MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS

	HAQ response at 3 months		HAQ response at 6 months	
	Univariable logistic regression OR (CI 95%), p-value (n = 36 to 65)	Multivariable logistic regression OR (CI 95%), p-value (n = 65)	Univariable logistic regression OR (CI 95%), p-value (n = 58 to 87)	Multivariable logistic regression OR (CI 95%), p-value (n = 87)
Gender (female)	0.074 (0.009,0.608), **p=0.015**	0.074 (0.009,0.608), p=0.015	0.138 (0.029,0.654), **p=0.013**	0.138 (0.029,0.654), p=0.013
Age	0.962 (0911,1.015), p=0.158		0.998 (0954,1.044), p=0.936	
Disease duration until first biologic	1.025 (0.950,1.106), p=0.525		0.998 (0.945,1.054), p=0.937	
Educational level (years)	0.938 (0.805,1.094), p=0.415		0.964 (0.838,1.109), p=0.609	
Body mass index (kg/m^2)	1.160 (0.793,1.696), p=0.445		1.126 (0.884,1.434), p=0.335	
Current smoking	0.857 (0.149,4.922), p=0.863		1.680 (0.188,14.981), p=0.642	
Extra-articular manifestations	1.613 (0.445,5.851), p=0.467		1.650 (0.478,5.701), p=0.429	
Methotrexate use	1.057 (0.285,3.928), p=0.934		1.469 (0.436,4.946), p=0.535	
Swollen joints (28-count)	0.942 (0.810,1.095), p=0.437		0.962 (0.817,1.133), p=0.646	
Tender joints (28-count)	0.923 (0.842,1.012), p=0.087		0.950 (0.871,1.036), p=0.246	
PGA (VAS-scale)	0.983 (0.956,1.012), p=0.248		1.012 (0.986,1.039), p=0.377	
CRP (mg/dl)	1.372 (0.899,2.095), p=0.143		0.962 (0.782,1.183), p=0.714	
ESR (mm/h)	1.003 (0.983,1.024), p=0.762		0.999 (0980,1.018), p=0.914	
DAS28-3V-ESR	0.742 (0.457,1.205), p=0.227		0.730 (0.448,1.189), p=0.206	
HAQ	0.712 (0.271,1.869), p=0.490		1.174 (0.521,2.644), p=0.699	

VAS-scale – Visual Analogic Scale; CRP – C Reactive Protein; DAS28-3V-ESR - Disease Activity Score 28, 3-variables; ESR – Erythrocyte Sedimentation Rate; HAQ – Health Assessment Questionnaire; EULAR - European League Against Rheumatism; OR – Odds Ratio; # – not selected during multivariable logistic regression analysis

95% CI 0.34, 0.78). In the same study, regarding DAS28 remission, females were also less likely to achieve disease remission, in both univariable and multivariable models (adjusted OR 0.34, 95% CI 0.21, 0.57)[18]. Saber et al. studied a total of 152 PsA patients and found that an increased DAS28 response was independently associated with male gender and patient-derived indices including HAQ, patient global VAS and early morning stiffness. However, linear regression analysis of baseline characteristics suggested that HAQ at baseline was the sole predictor of DAS28 at one year, not sustaining the effect of gender on the response to TNF blockers in this analysis[19]. The influence of gender was also observed with other outcomes measures,

namely drug survival. Glintborg et al. included baseline disease parameters and patient characteristics in a Cox regression analysis for TNF blockers drug survival. Female gender was associated with shorter TNF blocker drug survival [Hazard Ratio (HR) 1.42, 95% CI 1.11, 1.80] [17].

A HAQ response was also less probable in females, in our study. The association between female gender and HAQ scores had already been suggested in other studies. Husted et al. assessed predictors of physical functioning over the course of PsA, by investigating transitions between predefined states of the HAQ, and reported that female gender predicted faster decline in disability[20]. Tillett et al. reported that female gender predicted worse HAQ scores after 10 years from the onset of PsA[21]. However, this was the first study showing differences on HAQ response to TNF blockers associated with gender of PsA patients.

A similar effect of female gender as a predictive factor of poor response to TNF blockers had already been described in ankylosing spondylitis and rheumatoid arthritis[22]. The reasons remain unknown, however, several hypotheses such as sex hormones and musculoskeletal performance have been proposed. A relationship between higher testosterone levels and the presence of HLA-B27 have been reported in spondyloarthritis and this characteristic could play a role on disease activity. However, the mechanism which could be responsible for a better response to TNF blockers in those patients remains unknown[23, 24]. Another possible contributing factor may be related to the higher prevalence of concomitant generalized pain syndrome/fibromyalgia in the female gender[25]. This could be an important contributing factor as fibromyalgia-associated pain and fatigue are significantly more frequent in patients with PsA compared to controls[26].

We found that a moderate or good EULAR response at 6 months was more probable in patients using methotrexate at baseline. Glintborg et al. included baseline disease parameters and patient characteristics in a Cox regression analysis for TNF blocker drug survival. The lack of concomitant MTX use was associated with worse results with this surrogate outcome measure (HR 1.37, 95% CI 1.07, 1.75)[17]. Kristensen et al. studied 261 patients with active PsA, starting TNF blocker therapy for the first time in southern Sweden (from the South Swedish Arthritis Treatment Group register). Concomitant MTX (HR 0.64, 95% CI 0.39-0.95), etanercept and CRP levels at treatment initiation were associated with better overall drug survival. The improved drug survival with concomitant MTX appeared to be related to significantly fewer dropouts because of adverse events (HR 0.24, 95% CI 0.11, 0.52)[27]. In summary, the use of MTX had already been shown to be associated with TNF blocker drug survival; however this is the first time that an association with a better clinical response is reported. The underlying mechanism for this association is unknown. One of the hypotheses for this observation could be the prevention of development of autoantibodies to TNF blockers – however this hypothesis remains controversial and unproven. On the other hand, a recent meta-analysis did not show any statistical difference between monotherapy and concomitant use of MTX when analyzing ACR20, ACR50 and ACR70 as response measures[28]. It seems that this mechanism could play an important role on the immunogenicity; however, his influence is more established in rheumatoid arthritis than in PsA.

In some of the outcomes analyzed in our study, we also found better responses in patients with longer disease duration until first biologic and lower disease activity at baseline, as indicated by lower ESR, TJC and DAS28 3V-ESR. These observations could be explained by the difficulty to induce remission in PsA patients with highly active disease. They could also be spurious associations and previous literature has shown conflicting results.

Several other predictors of response were proposed to explain TNF blockers outcomes in PsA patients. However, Maneiro et al., in a recent meta-analysis, found some predictors of response to TNF blockers in AS, but no robust predictors of response in PsA were identified. Despite of several studies suggesting poorer response in women, this association was not confirmed in this meta-analysis[28].

The most important limitation of our study is the missing data that led to exclusion of a large number of patients treated with TNF blockers in the Reuma.pt registry. This may have resulted in selection bias and/or loss of power to detect some associations. Another limitation is related to the missing data regarding all variables included in the CASPAR classification criteria, which forced the investigators to use solely the diagnosis of PsA made by the rheumatologist. This limitation may be attenuated given that the diagnosis by the rheumatologist is often the gold-standard in classification criteria studies. It is important to acknowledge that the outcomes used were primarily made to evaluate rheumatoid arthritis (albeit being validated in PsA) and that they can be less precise in PsA. One of the

strengths of our study is the large number of response outcomes that were analyzed and the real-life setting of Reuma.pt.

In conclusion, we found that gender was the most consistent predictor of response to the first anti-TNF therapy, across different response measures, in patients with polyarticular PsA, with males having a higher probability of response than females. These findings suggest that gender-related biochemical, hormonal and psychological factors could play an important role on the response to anti-TNF therapy in PsA.

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