1) Title

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

2) Introduction

2.1) Background

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease affecting the skin and the joints. TNF-α blockers (adalimumab, etanercept, golimumab and infliximab) were a breakthrough development in the treatment of PsA. These agents have been found to be effective in controlled clinical trials for several aspects of the disease, including peripheral arthritis, psoriasis, enthesitis, dactylitis, as well as in preventing radiographic damage. (1)(1-6)

According to the Portuguese recommendations for the use of biological therapies in patients with psoriatic arthritis, patients should be considered candidates to biological therapy when 5 or more swollen joints (in a 66 joint count) are present on two separate occasions at least 1 month apart, after failure of conventional therapies, defined as an absence of response to treatment with at least one synthetic DMARD (methotrexate, sulfasalazine, leflunomide, cyclosporine) for at least 3 months on a standard (full) target dose, unless there is intolerance, toxicity or contra-indication.(7)

The use of predictors of response could help clinicians to make evidence-based decisions that maximize the benefits from treatment by targeting subsets of patients most likely to respond, at the early stages of the decision process. Predicting a good response might aid decision-making and improve the cost/benefit and benefit/risk ratios in patients selected to start anti-TNFα therapy.

A cohort analysis of patients who were followed prospectively in a PsA clinic (n=95) found that only the number of swollen joints at baseline was positively associated with the response of active joint counts at 12 months [odds ratio (OR) = 1.34; p = 0.02]. In this study, past use of TNF-α blockers was negatively associated with response (OR = 0.05; P = 0.01).(8)

An analysis of a prospective patient cohort attending a biologic clinic, which included 152 PsA patients found that post-treatment remission (defined by a DAS28-CRP < 2.6) was most strongly associated with baseline HAQ.(9) Recently, obesity was found to be a negative predictor of the clinical response of PsA patients to TNF-α inhibitors.(10) However, another recent study showed that disease activity and clinical response to anti-TNF-α therapy in PsA do not seem to be affected by BMI.(11) These contradicting results suggest that further prospective studies are needed to better understand the relationship between obesity and response to anti-TNFα drugs in PsA patients.

A study including 764 patients with PsA from a prospective nationwide rheumatic diseases database, the Danish biologics registry (DANBIO), found that an increased CRP level at baseline was the sole factor linked to clinical response and treatment continuation.(12) Similar results have been reported by other authors regarding patients with PsA as well as patients with RA and patients with spondyloarthritis.(13-17)

In a prospective, 12-week, open-label, uncontrolled study to evaluate the effectiveness of adalimumab in 442 patients with PsA and identify predictors of good clinical response, the authors concluded that lower impairment of physical function, greater pain, male sex and no systemic treatment with glucocorticoids were factors that increased the chance of achieving a good clinical response.

Three response criteria are in use for PsA: the PsA response criteria (PsARC) developed specifically for PsA and the ACR and EULAR response criteria originally developed for RA. All three response criteria can discriminate placebo from active treatment in clinical trials.(18) In this study, we will use the EULAR response criteria and PsARC and we will include only PsA patients with polyarticular involvement (with or without axial involvement) since this is the group of PsA patients where the validity of the PsARC and DAS/DAS28 has been consistently shown.

3) Aims of the proposed study

To determine predictors of response after 3 and 6 months of treatment with anti-TNFα in patients with polyarticular involvement (with or without axial involvement).

4) Methods

4.1) Database

Data will be collected from the Rheumatic Diseases Portuguese Registry (Reuma.pt), which is a national prospective longitudinal multicenter cohort initiated in 2006. It captures more than 90% of patients treated with biologic therapies managed in rheumatology departments across Portugal.(7, 19)

4.2) Inclusion and Exclusion criteria

Inclusion criteria: Anti-TNFα-naive patients with PsA with at least 3 months of follow up after the beginning of anti-TNFα therapy.

Exclusion criteria: Patients with oligoarticular or mutilant forms of PsA.

4.3) Response measures

A) Primary response measure: the primary response measure will be a "good" EULAR clinical response (Table 1).

Table 1. EULAR response criteria

DAS28 at end point	Improvement in DAS28 from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good	Moderate	None
>3.2 and ≤5.1	Moderate	Moderate	None
>5.1	Moderate	None	None
DAS28, 28-joint Disease Activity Score.			

B) Secondary response measures:

B1) EULAR moderate-good response: please see table 1.

B2) PsA Response Criteria (PsARC): The PsARC is defined as improvement in at least two of the following 4 criteria, one of which must be joint swelling or tenderness, and no worsening in any of the 4 measures: (1) 20% or more improvement in physician global assessment of disease activity; (2) 20% or more improvement in patient global assessment of disease activity; (3) 30% or more improvement in tender joint count; and (4) 30% or more improvement in swollen joint count.(20)

B3) DAS28 remission: DAS28 <2.6.

B4) Minimal Disease Activity (MDA) according to GRAPPA: Patients are classified as achieving MDA if they fulfil 5 of 7 outcome measures: tender joint count ≤1; swollen joint count ≤1; psoriasis activity and severity index ≤1 or body surface area ≤3; patient pain VAS score ≤15 (0-100 scale); patient global disease activity VAS score of ≤20; HAQ score ≤0.5; and tender entheseal points ≤1.

B5) The HAQ will also be used as a measure of response: achievement of a HAQ ≤0.5 and/or a decrease in the HAQ ≥0.22 (proposed by some authors as being the minimal clinically important difference in the HAQ score).

4.4) Statistical analysis

Variables will first be selected for univariate logistic regression analyses with 3-month and 6-month response criteria as the dependent variable. Different models will be built for each response criteria (primary and secondary response measures).

Age, sex, disease duration, baseline CRP/ESR, HLA-B27 status, smoking (ever/never), educational level, alcohol consumption (less/more than 3 units per day), BMI, presence of rheumatoid factor (RF), treatment with glucocorticoids, treatment with DMARDs, presence of dactylitis/enthesitis, baseline total tender joint count (TJC) and total swollen joint count (SJC), baseline physical function (HAQ), baseline disease activity (DAS28), patient global assessments and the anti-TNFα used (infliximab, adalimumab, etanercept or golimumab) will be considered in univariate analysis.

Relevant variables will then be included in subsequent multivariate logistic regression analysis models, and non-significant variables will be removed from the model one at

the time (starting with the least significant variable), checking for confounding, in order to achieve optimal model-fit. Interactions will be tested.

5) Study Limitations

The most important limitation of this project could be the missing data that could lead to bias. Reuma.pt has 452 PsA patients under biologic treatment. There is the risk of the study being underpowered.

6) Calendar

The project will start in April 2015 and will be developed during 1 year after receiving the database. Submission to relevant rheumatology conferences is anticipated (National SPR Congress, EULAR and ACR Congress).

7) Budget

Financial support is not being requested to Reuma.pt/SPR.

8) Conflicts of Interest

The research team declares no conflicts of interest.

9) Reseach team

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10) References

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