

## 1. Title

EARLY PsA – Effectiveness of early Adalimumab therapy in psoriatic arthritis patients from Reuma.pt, the Rheumatic Diseases Portuguese Register, Portuguese Rheumatology Society (SPR)

## 2. Background

Patients with psoriatic arthritis (PsA), have a chronic systemic inflammatory disorder, with peripheral arthritis and skin manifestations including axial disease, dactylitis, enthesitis, skin and nail psoriasis, with consequent adverse impact on function and quality of life (QoL). The joint and skin manifestations associated with PsA are remarkably heterogeneous in the extent and type of tissue involved <sup>(1-7)</sup>.

The prevalence of psoriasis has been estimated between 2% and 3% and the estimated prevalence of inflammatory arthritis among patients with psoriasis has varied widely from 6% to 42% <sup>(3)</sup>. Psoriasis usually precedes the development of arthritis by several years <sup>(8,9)</sup>

Heterogeneity is observed not only in disease manifestations, but also in severity and in the course of the disease <sup>(3,7)</sup>.

The disease burden could be significant, since up to 20% of PsA patients will have a progressive and disabling form of arthritis <sup>(3,4)</sup>. In terms of economic and quality-of-life burden to patients and society, and due to physical function limitations imposed by PsA, indirect costs such as disability and lost productivity are substantial drivers of the total costs of care <sup>(10)</sup>. Data available is sometimes conflicting, but cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, Crohn's disease, ophthalmic disease, depression and anxiety are common comorbidities associated with PsA <sup>(11)</sup>

To improve management of the disease, a treatment to target strategy, aiming at remission or low disease activity, and an early diagnosis are important to avoid and control joint damage <sup>(12)</sup>.

Early detection of PsA signs and symptoms with a rapid therapeutic intervention reduces the risk of clinical progression <sup>(13)</sup>. As for PsA treatment patterns, these generally mirrored those for RA. However, based on pathologic and clinical features that are distinct, it does not necessarily follow that treatment results will be the same <sup>(14)</sup>. Thus, methotrexate (MTX) was reported as the most commonly used disease-modifying drug (DMARD) (39% of PsA patients) in monotherapy or in combination with other conventional DMARDs (csDMARDs) or biologic DMARDs <sup>(15)</sup>.

In the ADEPT trial, ACR20, ACR50, and ACR70 response rates did not differ between patients taking adalimumab in combination with MTX and patients taking adalimumab alone. For patients receiving combination therapy, the ACR20, ACR50, and ACR70 response rates were 55%, 36%, and 17%, respectively, at week 12. For patients receiving monotherapy, the response rates were 61%, 36%, and 23%, respectively. Similar response rates were observed at week 24 in these 2 groups <sup>(16)</sup>. In one study about the impact of MTX on anti-TNF treatment in PsA, the authors concluded that in both, axial and peripheral involvement of PsA, co-medication of MTX added to treatment with ADA has no relevant impact on efficacy, safety or treatment adherence, however, randomized controlled trials (RCTs) are needed to confirm the data <sup>(17)</sup>.

There is also a need of evidence, in PsA, that early versus delayed treatment with csDMARDs is beneficial in the long-term <sup>(18)</sup>. One study reported that anti-TNF therapy was effective in treating patients with shorter PsA duration. In this study, the patients had minimal skin involvement and results were not compared with patients with longer disease duration <sup>(13)</sup>. In another recent study, that examined the influence of PsA disease duration on the

response to etanercept in patients with PsA plus moderate-to-severe psoriasis, was shown that although PsA patients responded to biologic DMARD treatment irrespective of disease duration patients with shorter PsA duration had greater improvements in arthritis scores and several patient reported outcomes (PRO) measures<sup>(19)</sup>. The role of biologic DMARDS in early PsA is therefore still unclear<sup>(20, 21)</sup>.

## Rationale

There is a lack of evidence on the effect of ADA treatment in early treatment of PsA patients and the effect of concomitant use of conventional DMARD's on the disease course.

This nested case-control study aims to analyse all PsA patients registered on the Rheumatic Diseases Portuguese Register (Reuma.pt) on treatment with adalimumab (ADA), in order to evaluate the possible effect of ADA in patients treated earlier (<5 years of symptoms duration) and the potential effect of concomitant conventional DMARDs, on clinical and functional outcomes. These real world data could allow us to show the benefit of early treatment with adalimumab ± conventional DMARDs in PsA patients.

## 3. Study Objectives

- The main aim of the study is to compare the clinical outcomes among PsA patients receiving adalimumab, with short and long disease duration between June 2008 and September 2015.

The primary objectives are:

- 1) To compare the clinical outcomes among PsA patients receiving adalimumab, with short and long disease duration between June 2008 and September 2015.
- 2) To compare the clinical outcomes among PsA patients receiving adalimumab with vs without concomitant therapy with conventional DMARDs, between June 2008 and September 2015.
- 3) To compare the patient reported outcomes (work status,) among PsA patients receiving adalimumab, with short disease duration and long disease duration between June 2008 and September 2015.

This is a retrospective study. Therefore it is not designed to identify or quantify a safety hazard relating to an authorized medicinal product.

## 4. Methods

This retrospective study will be performed in a retrospective cohort design, non-interventional, multi-center format.

The study population will consist of adult PsA patients who have been registered on the Rheumatic diseases Portuguese Register (Reuma.pt) on treatment with adalimumab.

Treatment, procedures and diagnostic methods have followed physicians' routine clinical practice.

The data will be documented from the Reuma.pt registry. No patient identifiable information will be captured.

Study Population:

Patients with Psoriatic arthritis: diagnosis verified by CASPAR classification criteria<sup>(22)</sup>

- a. PsA adult patients (age ≥18 years old), both gender, that have received adalimumab therapy for at least 6 months

- b. Patients who have ever been diagnosed with rheumatoid arthritis or other inflammatory arthropaties, will not be included.

### Description of variables

**Demographic data** - The patient's demographic data (including year of birth, gender, race, and ethnicity, height and weight).

**Swollen Joint Count (SJC) and Tender Joint Count (TJC)** - Recorded data on patient's swollen and tender joints per standard of care.

**Patient Global Health Assessment and Physician Global Disease Assessment** - Recorded data on patient's and physician assessment of disease per standard of care.

**Psoriasis Area and Severity Index (PASI)** - Recorded data on patient's Psoriasis Area and Severity Index (PASI) per standard of care. (if available)

**Erythrocyte Sedimentation Rate / C-Reactive Protein (ESR/CRP)** - Recorded data on patient's ESR and/or CRP, with the respective units, per standard of care.

**Extra articular manifestations**- Recorded data on patient's extra articular manifestations related with PsA.

**Co-morbidities** - Recorded data on Hyperuricemia, Arterial Hypertension, Diabetes Mellitus, Dyslipidemia.

**Work Status** - Recorded data on patient's work status. Work status as defined on Reuma.pt: Full time work, part-time work, in house work, medical leave greater than one month, unemployed and retired.

**Health Assessment Questionnaire (HAQ) and EQ-5D** - Recorded data on patient's HAQ and/or EQ-5D, if available.

**Concomitant therapy** – conventional DMARDs, corticosteroids, NSAIDs

Table 1. Scheme of data collection per this research plan.

Study Activity	GENERAL DATA	PROs	MUSCULO-SKELETAL SIGNS	SKIN SIGNS
Socio-demographic data	X			
Concomitant therapy	X			
Comorbidities	X			
BMI	X			
HAQ-DI		X		
EQ-5D		X		
PtGA (VAS)		X		
Verification of PsA diagnosis (CASPAR)			X	
TJC/SJC (66/68)			X	X
DAS28 by individual components			X	
Enthesitis (count) (if available)			X	
Dactylitis (count) (if available)			X	
PGA (VAS)			X	
CRP /ESR (if available)			X	
PASI (if available)				X
Extra-articular manifestations			X	

## **Ethics and Quality**

This retrospective study will be run in compliance with Portuguese laws and regulations. The protocol will be submitted to the Local Ethics Committee.

The guidelines for good pharmacoepidemiology practices (GPP) in non-interventional studies will be respected. This trial is not in the scope of Good Clinical Practice (GCP) studies.

Subject confidentiality is assured; only anonymized data will be collected. In order to protect patient's identity, a unique number will be assigned to each patient and related study records.

## **5. Data Analysis Plan**

### **Endpoints**

Research outcomes of primary interest:

- To compare the clinical outcomes, measured by Psoriatic Arthritis response criteria (PSARC), among PsA patients receiving adalimumab, with short and long disease duration between June 2008 and September 2015.
- To compare the clinical outcomes, measured by Psoriatic Arthritis response criteria (PSARC), among PsA patients receiving adalimumab with vs without concomitant therapy with conventional DMARDs, between June 2008 and September 2015.
- To compare the patient reported outcomes (work status,) among PsA patients receiving adalimumab, with short and long disease duration between June 2008 and September 2015.

Research outcomes of secondary interest:

- Adalimumab PsA patient's characteristics, extra-articular manifestations and comorbidities, at baseline, and work status and EQ-5D health status at baseline.
- The proportion of adalimumab PsA patients, that achieve PSARC, the average time to achieve it, and maintaining it after 6 and 12 months
- Adalimumab PsA patient's work status and EQ-5D health status after 12 months of treatment with adalimumab.

### **Statistical Analysis**

The following clinical outcome measures will be assessed to determine the overall response rate to adalimumab treatment:

- a) Proportion of PsA patients achieving and maintaining Psoriatic Arthritis response criteria (PSARC).
- b) Time from first use of conventional DMARD to biologic initiation with adalimumab and the time from first use of biologic DMARD to switch to adalimumab.
- c) Work status of PsA patients receiving adalimumab
- d) To evaluate baseline characteristics in patients with PsA at enrolment.
- e) To describe the quality of life of PsA patients treated with adalimumab.

Collected data will be summarized by descriptive statistics.

Data from all clinical assessments of the patients will be summarized using the Kaplan-Meier method, descriptive statistics and multivariate regression analysis.

Descriptive statistics of adalimumab PsA patients, that achieve PSARC, average

time to achieve it, and maintaining it after 6 and 12 months, of adalimumab PsA patient's characteristics, extra-articular manifestations and comorbidities, at baseline, and work status and EQ-5D health status at baseline and after 12 months of treatment with adalimumab.

The Kaplan-Meier method will be used to estimate the median time (95% Confidence Interval) to estimate time from first use of conventional DMARDs to biologic initiation with adalimumab, and from first use of biologic to switch to adalimumab.

Regression analysis will be done for disease duration and clinical outcome, for conventional DMARD concomitant therapy and clinical outcome, and for disease duration and work productivity as explanatory variables.

**Sample Size Calculation**

The study is exploratory in nature and we assume no pre-specified hypotheses about statistical significance and/or direction of correlations. There is thus no need for power calculation, but we assumed that a total of approx. 195 patients are sufficient to provide statistically stable estimates of the correlations between specify characteristics observed.

**6. Timeline**

Estimated duration of data collection and analysis is 3 months.

Activity	months				
	1	2	3	4	5
Variables Selection and Extraction					
Database Cleaning					
Statistical Analysis					
Final Report					

**7. Proponent**

Helena Santos Carneiro

**Institutions**

The project is open to all National Centers interested to cooperate

**Co-authors**

All clinicians who actively work on the project will be co-authors with a maximum of 3 co-authors per participating institution

**8. Financial support and conflict of interests**

This study received financial support from Abbvie. There are no conflicts of interest

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