1. Title: Real World Effectiveness of Switching between tumor necrosis factor inhibitors (TNFi) in Psoriatic Arthritis – EXCHANGE PsA

2. Background

The development of tumor necrosis factor inhibitors (TNFi) therapies lead to a dramatic improvement in the management of Psoriatic Arthritis (PsA). TNF acts in the early stages of the inflammatory cascateby stimulating T-cell activation and induces the expression of interleukin 2 (IL-2), interferon gamma (IFNγ) receptors, proinflammatory cytokines (like interleukin 1 and IL-2) and proinflammatory chemokines (like interleukin 8) (1). More recently IL-23/IL-17 has also been largely implicated in the pathogenesis of psoriasis (PsO) and PsA. In the literature we can find abundant evidence on the efficacy of TNFi and therapeutic agents blocking IL12/23 and IL17 in the treatment of patients with PsA (2-5).Their role in the management of PsA is also recognized by the European League Against Rheumatism (EULAR) recommendations (6) and in the National Guidelines endorsed by the Portuguese Society of Rheumatology (7). Despite the effectiveness of these agents, there is still a significant proportion of patients that do not respond to and/or do not tolerate treatment (8-10). Clinical recommendations suggest that switching between TNFi when faced with lack of efficacy and/or toxicity should be considered (6-7), although real world research shows reduced drug survival rates and poorer responses after switching (8-10). Considering that predominant physiopathologic pathways might vary between patients, changing patients to drugs with different mechanisms of action could bring additional benefits aiming at more personalized decisions.

Study rational

Given that there is limited evidence from clinical trials on the efficacy of switching to a another TNFi when faced with lack of efficacy and/or toxicity, and that there is lack of Portuguese data on the real world effectiveness of this practice, it is crucial that new

research is undertaken to generate additional evidence on this field. The results from this work will contribute to clarify the rates of response after first TNFi switching in PsA Portuguese population and assess drug survival in this context.

3. Study hypothesis

- The effectiveness of TNFi, measured by drug survival and response rates within a period of 4 years of treatment, is reduced in patient with previous TNFi exposure.

3.1 Objectives

Assess the effectiveness measured by drug survival and response rates within a period of 4 years of treatment in patients with PsA treated with TNFi, according to the number and type of previous DMARDs. Investigate frequency and main reasons for switching between TNFi in Portuguese patients with PsA diagnosis registered at Reuma.pt.

Primary objective

Assess drug survival rates in patients treated with a first TNFi.

Secondary objectives

- Assess drug survival rates in patients treated with a second and third or more TNFi;
- Identify reasons for treatment discontinuation (loss of effectiveness, adverse event, remission, other) in patients treated with a first, second and third or more TNFi;
- Assess treatment response rates in patients treated with a first, second and third or more TNFi.

- Determine predictors of persistence of TNFi;
- Determine predictors of response to TNFi

Primary endpoints

- Drug survival rate for a period of 4 years of treatment in patients treated with a first TNFi;

Secondary endpoints

- Drug survival rate for a period of 4 years of treatment in patients treated with second, third or more TNFi;
- Reasons for switching (loss of effectiveness, adverse event, remission and other) at 3, 6 and 12 months and every year of treatment thereafter;
- Response rate measured by DAS28 responses (good EULAR responses), ACR responses (20/50/70), PsARC response, PsAJAI, ΔHAQ-DI and ΔSF-36 responses at 3, 6 and 12 months and every year of treatment thereafter, for patients with peripheral involvement;
- Minimal disease activity rates as defined by the minimal disease activity (MDA) index
- Response rate for axial disease measured by ASDAS (ΔASDAS≥1,1), BASDAI (ΔBASDAI≥50% or ΔBASDAI>2) at 3, 6, and 12 months and every year of treatment thereafter, for patients with axial involvement;

4. Methodology

This is a retrospective non-interventional study of patients with diagnosis of PsA using real world anonymous patient-level data from the Reuma.pt database. Electronic clinical records will be retrieved for all patients that fulfill the study inclusion criteria.

Reuma.pt (www.reuma.pt), the Rheumatic Diseases Portuguese Register, became active in 2008 and includes patients with varied rheumatic diseases (rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, vasculitis and auto-inflammatory syndromes). Currently more than 70 centers (public and private) participate in the registry.

Definitions

Drug survival is defined as the time until treatment discontinuation.

Discontinuation is defined as either one of the following events:

- End of treatment – 90-day continuous gap of treatment without a posterior biological treatment;
- Switch –occurrence of any switch to another biological agent.
- Temporary discontinuations of <90 days (which is common for surgery or certain adverse events, for example, infection), after which the patient restarted the same biological agent, are counted as continuous use of the drug.

Variables

Table 1. Variables to be collected

Variables to be collected	
Baseline patient characteristics	• Demographic and clinical characteristics (gender, age, education, smoking, alcohol consumption, BMI) • Date of first symptoms • Date of diagnosis of PsA • Subtype of PsA and type of involvement (peripheral, enteseal and axial) and/or axial involvement. • HLAB27, RF, ACPA • Time from diagnosis to 1st DMARD • Time from diagnosis to 1st bMARD, • Presence of dactylitis • Presence of enthesitis, MASES and SPAARC scores • Presence of extra-articular manifestations (PsO, uveitis, IBD) • Presence of comorbidities (obesity, diabetes, CVD) • DAS28, HAQ-DI, PASDAS • BASDAI, ASDAS, BASFI • VAS patient/pain/physician • CRP; ESR • Comorbidities (hypertension, dyslipidemia,, cardiovascular diseases, diabetes, malignancies, lymphomas, , uveitis) • PASI score • PsA therapy (cs and DMARD)
At follow-up (to be collected for each biological DMARD used per patient, at 3, 6 and 12 months and every year thereafter)	• Biological DMARD • Starting date of treatment • Dose used • Frequency of administration • Concomitant treatment during biologic therapy (csDMARDs, corticosteroids, NSAIDs, others) • DAS28, HAQ-DI • ACR 20/50/70 • PsARC response • PsAJAI • BASDAI, ASDAS, BASFI • ASAS 20/40 • VAS patient/pain/physician

	• CRP; ESR • Discontinuation date • Reason for discontinuation

Statistical analysis:

Drug survival will be assessed by Kaplan-Meier survival analysis.

Data source:

This study will use secondary data collection from the Reuma.pt database (no data on patient identification will be collected).

Population:

Target population: Patients with diagnosis of PsA (peripheral or axial) registered in the Reuma.pt database exposed to TNFi treatment.

The study will include all patients identified as PsA patients that fulfill the following inclusion criteria:

- Age ≥ 18 years old;
- Confirmed diagnosis of PsA according CASPAR criteria
- Register of at least 1 prescription of TNFi;
- Minimum set of data that can be used to assess treatment response, switch and drug survival.

Patients that do not fulfill the inclusion criteria will be excluded from the study.

Sample size justification:

The 2015 Reuma.pt annual report (11) had 1.355 patients registered with PsA diagnosis, and 530 bDMARDs.

Expanding the scope of the analysis

It is expected that the use of other bDMARDs in PsA will increase in the future. Although there is evidence form RCTS on the efficacy of these drugs there is still a need to generate data on the effectiveness of the bDMARD on everyday practice.

Expanding the scope of the analysis to include these patients would provide an added value to the study and would generate valuable evidence on the real world effectiveness of these drugs.

5. Study limitations

This is a retrospective non-interventional study using patient-level data from a database. The main limitation associated to the study methodology is the existence of missing data that could lead to bias.

6.Calendar

It is estimated that it will take 12 months to extract the data, perform the statistical analysis, quality check the calculations and results, and prepare the study final report.

Research team

Proponentes: Elsa Vieira de Sousa, Mónica Eugénio, Maria José Santos

Rheumatologist from all collaborating centers according to Reuma.pt guidelines up to a maximum of 3 per centre.

Institutions

The project is open to all National Rheumatology Centrs interested in cooperating.

Co-authors

Authorship and co-authorship will be based in the International Committee of Medical Journal Editors and Reuma.pt guidelines. (12).

Budget

The project is funded by a research grant from Novartis Farma Produtos Farmacêuticos S.A.

Conflict of interest

To be completed after research team is identified

Ethical considerations

This study will be conducted according to the Declaration of Helsinky and the International Guidelines for Ethical Review of Epidemiological Studies. This study will be submitted for validation and approval to the Coordinator and Scientific Board of Reuma.pt. Results will be presented in an objective way, and will not be hidden or manipulated.

References

(1) Ritchlin CT: Pathogenesis of psoriatic arthritics. Curr Opin Theumatol 2005, 17:406-412.

(2) Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150–7.

(3) Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60:976–86.

(4) Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264–72.

(5) Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52:3279–89.

(6) Gossec L, Smolen JS, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacologic therapies. Ann Rheum Dis 2012; 71:4-12

(7) Vieira-Sousa E, M Machado P, Costa J, Ribeiro A, et al. Portuguese recommendations for the use of biological therapies in patients with psoriatic arthritis – 2015 update. Acta Reumatol Port. 2015;40:275-290.

(8) Saad AA, Ashcroft DM, et al. Persistence with anti-tumor necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Research & Therapy, 2009; Vol 11, No 2

(9) Fagerli KM, Lie E, et al. Switching between TNF inhibitors in psoriatic arthritis: data from the NOR-DMARD study. Ann Rheum Dis 2013; 72:1840-1844

(10) Glintborg B, Ostergsrrd M, et sl. Clinical Response, Drug Survival and Predictors Thereof Among 548 Swithers of Tumor Necrosis Factor Alpha Inhibitor Therapy in Psoriatic Arthritis. Results From the Danish Nationwide Danbio Registry. Arthritis Rheum 2012; 64 Suppl 10: 2558

(11) Sociedade Portuguesa de Reumatologia. Relatório de Execução 2015. Accessed October 2015. Available at http://www.reuma.pt/docs/Reumapt_relatorio_execucao_201512.pdf

(12) International Committee of Medical Journal Editors. Accessed October 2015. Available at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html