1. Title:

Comparative long-term effectiveness and safety of switching to alternative tumour necrosis factor antagonists, tocilizumab or rituximab in patients with rheumatoid arthritis and inadequate response to a first-line TNF inhibitor

2. Background:

The treatment of Rheumatoid arthritis (RA) has advanced in terms of controlling the disease since the development of biological disease-modifying antirheumatic drugs (bDMARDs), improving the symptoms and the progression of joint damage, with a good safety profile[1].

Tumour necrosis factor inhibitors (TNFi) are highly effective treatments for active RA. However, up to 40% of patients either fail to respond adequately to TNFi (primary inefficacy) or lose responsiveness over time (secondary inefficacy)[2]. Options available to patients with an inadequate response to TNFi include treatment with an alternative TNFi or switching to a biological therapy with a different target as Tocilizumab (TCZ), a monoclonal antibody targeting the interleukin-6 receptor, Rituximab (RTX), an anti-CD20 B-cell-depleting therapy, or abatacept (ABA), a selective co-stimulation modulator[3]. Data about the comparative effectiveness of different switching strategies are, however, limited. After a first TNFi failure, a second-line TNFi appears to be more likely to fail earlier than non-TNFi[4–6]. In the absence of head-to-head trials, the effectiveness of different strategies has been studied in routine clinical practice in observational trials at 6 or 12 months, with no data for long-term effectiveness. There are a few observational studies comparing the short-term effectiveness of a subsequent TNFi *versus* non-TNFi[1,3,7–13]. A Bayesian network meta-analysis involving 1796 patients found that TCZ 8 mg was the second-line non-TNF biologic with the highest performance regarding an early good response at 6 months based on ACR20 response and acceptable safety profile, followed by RTX, abatacept and tofacitinib, and none of these options was associated with a significant risk of withdrawal due to adverse events (AEs).[3] TCZ in combination with DMARDs or as monotherapy resulted in significantly more patients achieving remission and more marked improvements in patient-reported outcomes compared with TNF inhibitors in patients with inadequate response to DMARDs and/or TNFi treated in routine clinical practice[7,8]. The studies comparing the short-term effectiveness of RTX with a subsequent TNFi have suggested that the response rates of patients switching to a second or third TNFi are lower than those treated with RTX and earlier initiation of RTX may lead to tighter control of the disease activity and improved outcomes in patents with an inadequate response to a TNFi[1,9–13].This difference was particularly evident among Rheumatoid Factor (RF) positive patients who discontinued their initial TNFi because of inefficacy[2]. Also, a predictive biomarker for the response to RTX may be the positivity to anti-cyclic citrullinated peptide antibodies (ACPA)[15]. RTX remains well tolerated over time and multiple courses, without significant safety risks or increased rates of adverse events with prolonged exposure[16,17].

The long-term effectiveness of RTX may be superior to the short time data, related with the known delay of the mechanism of action. RTX can be the most cost-effective treatment option in patients whose TNFi therapy failed, with even superior effectiveness and similar safety profile to other agents[18].

<u>Study rational:</u> There is limited evidence from long term clinical trials on the effectiveness of switching to another TNFi, RTX or TCZ when faced with failure of a TNFi. It is crucial that new research is undertaken to generate additional evidence in this field. REUMA.pt, the Rheumatic Diseases Portuguese Register, provides an excellent source of real world data on this subject that still has not been yet used. In Portugal, these three therapeutic options are the most frequently used, unlike others such as ABA. The results from this work will contribute to clarify the outcome after TNFi failure switching to RTX, TCZ or another TNFi in RA Portuguese population.

3. Study hypothesis:

- o The effectiveness of switching to RTX or TCZ, measured by persistency rates within a period of 5 years of treatment, is better than a switch to a second TNFi, in patients who failed previous TNFi.

3.1. Objectives

<u>Primary objective</u>

- o To compare the effectiveness and safety of RTX, TCZ and a second TNFi measured by stratified persistency rates within a period of 5 years, in RA patients with previous inadequate response to their first TNFi.

<u>Secondary objectives</u>

- o To compare the disease activity in patients who remained on RTX, TCZ and TNFi at 6 and 12 months and every year for a period of 5 years of treatment.
- o To compare the response rates of RTX, TCZ and TNFi at 6 months, 1 and 2 years.
- o To investigate the frequency and reasons for treatment discontinuation or switching (related to efficacy, safety, remission, other) throughout the treatment.
- o To compare the rates of adverse events (AEs) including serious and minor side effects in patients treated with RTX, TCZ and a second TNFi.

<u>Primary endpoints</u>

- o Retention rates of RTX, TCZ or TNFi therapy at 6 and 12 months and every year for a period of 5 years of treatment.

<u>Secondary endpoints</u>

- o Proportion of patients in remission, or at least low disease activity, according to Disease activity score-28 joints (DAS28), Clinical disease activity index (CDAI) and Simplified disease activity index (SDAI) in patients treated with RTX, TCZ or TNFi at 6 and 12 months and every year for a period of 5 years of treatment.

- Frequencies of EULAR good and good/moderate response for each treatment at 6 and 12 months and 2 years of treatment.

- Change in DAS28, erythrocyte sedimentation rate (ESR), C-reactive protein (CPR), tender joint count (TJC28), swollen joint count (SJC28) and visual analogue scale (VAS) at 6 and 12 months 2 years of treatment.

- Change in health assessment questionnaire (ΔHAQ) at 6 and 12 months and 2 years of treatment.

- Reasons for stopping the treatment (loss of effectiveness, adverse event, remission and other).

- AEs (serious and minor side effects) throughout the treatment.

4. Methodology

This is a non-interventional study of patients with diagnosis of RA and previous treatment failure to their first TNFi who have switched to a second TNFi, RTX or TCZ using real world anonymous patient-level data from the Reuma.pt database.

Definitions

- Remission: DAS28 <2.6, CDAI ≤2.8 and SDAI ≤3.3;

- Low disease activity: DAS28 <3.2, CDAI ≤10 and SDAI ≤11;

- Discontinuation is defined as either one of the following events:

      • Switch: occurrence of any switch to another biological agent.

      • End of treatment: 90-day continuous gap of treatment without a posterior biological treatment, for biological therapies other than RTX; RTX is considered as stopped at either the date of initiation of a new bDMARD, the date of registration of suspension for an AE or the date of death, whatever comes first.

      • Temporary discontinuations: <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;

- EULAR good response: change in DAS28>1.2 and DAS28≤3.2;

- EULAR good/ moderate response: change in DAS28>0.6 and DAS28≤5.1 or change in DAS28>1.2 and DAS28>5.1.

Variables

Baseline patient characteristics:

• Demographic and clinical characteristics (gender, age, education, smoking, alcohol consumption, body mass index);

• Date of first symptoms;

• Date of diagnosis of RA;

• RF and ACPA;

• Comorbidities (hypertension, dyslipidemia, cardiovascular diseases, diabetes, malignancies);

• RA therapy – current corticosteroids (CS) and conventional synthetic DMARDs (csDMARDs); previous csDMARDs;

• Time from diagnosis to 1st bDMARD;

• Visual analogue scale (VAS) patient/pain/physician;

• CRP and ESR;

• TJC and SJC;

• DAS28, CDAI, SDAI and HAQ.

At follow-up (to be collected for each bDMARD, at 6 and 12 months and every year thereafter):

• bDMARD;

• Starting date of treatment;

• Dose used and frequency of administration;

• Concomitant treatment during biologic therapy – csDMARDs, CS, nonsteroidal anti-inflammatory drugs (NSAIDs), others;

• VAS patient/pain/physician;

• CRP and ESR;

• TJC and SJC;

• DAS28, CDAI, SDAI and HAQ;

• Discontinuation date and reason for discontinuation;

• AE (serious and minor side effects) throughout the treatment.

Statistical analysis:

Descriptive analysis of continuous variables will be reported as mean and standard deviation, or median and quartiles in case of non-normal distribution, according to the biologic treatment.

Descriptive analysis of categorical variables will be displayed as frequency or proportions, according to the biologic treatment.

Baseline data will be compared between the three treatments groups using the chi-square test for categorical variables and ANOVA or Kruskal-Wallis tests for continuous variables.

Persistency of RTX, TCZ and TNFi will be estimated using Kaplan-Meier analysis, where follow-up time will be calculated as time in months from initiation of each therapy until discontinuation/ switch of this therapy and last follow-up visit.

Relative to disease activity, baseline and follow-up data at 6 months and every year of treatment will be compared according to biologic class using the chi-square test for categorical variables and t-student or Mann-Whitney tests for continuous variables. Follow-up categories will be defined as follows: 6 months, 1 year, 2 years, 3 years, 4 years and 5 years.

An univariate analysis with the independent variables (age, sex, seropositivity, number of disease duration, and baseline disease activity) and multiple logistic regression and propensity score-based

methods will be used to explore the relationship between biologic class and treatment response, to try to accommodate for patient- and disease-related-confounders.

Reasons for discontinuing therapy will be summarize using descriptive statistics and stratified by the treatment.

The safety analysis will be performed by calculating the cumulative adverse events in the end of the follow-up period.

P value will be considered significant at <0.05.

The SPSS v23 will be used to analyse the data collected from this study.

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 RA registered in the Reuma.pt database exposed to a second TNFi, RTX or TCZ treatment after previous TNFi failure.

The study will include all patients identified as RA patients that fulfil the following inclusion criteria:

• Age ≥ 18 years old;

• Confirmed diagnosis of RA according American College of Rheumatology (ACR) 1987 revised RA criteria;

• Minimum set of data that can be used to assess treatment response and switch.

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

5. Study limitations

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

6. Calendar

Timelines for the several steps of this project are presented in table II. Globally, it is estimated that it will take 5 months to be concluded.

Table II. Timeline

	Oct-Nov/2017	Dec/ 2017	Jan – Fev/ 2017
Data extraction	███████		
Data analysis		███████	
Prepare the study final report			███████

7. Research team

- Proponents: Daniela Santos Faria, Joana Leite Silva, Joana Rodrigues, Joana Sousa Neves, Daniela Peixoto, Filipa Teixeira, Sérgio Alcino, Carmo Afonso, José Tavares Costa - Rheumatology department Unidade Local de Saúde do Alto Minho;

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

Institutions: The project is open to all National Rheumatology Centers interested in cooperating.

Co-authors: Authorship and co-authorship will be based in the International Committee of Medical Journal Editors and Reuma.pt guidelines.

Conflict of interest: To be completed after research team is identified

8. 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 Ethics Committee. 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.

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