TITLE: **Drug survival analysis of biologic agents in rheumatoid arthritis and predictors of drug discontinuation in real world clinical practice**

BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory highly incapacitating disease that can lead to premature death. The pharmacological treatment for RA is aimed at reducing or minimizing the progression of the disease[1]. Several clinical trials have demonstrated that biological agents improve signs and symptoms of RA both in early and established disease, and that remission can be achieved not only in early disease, but also in established RA that responded inadequately to conventional disease-modifying antirheumatic drugs (DMARDs)[2,3]. Currently available biotechnological agents include the tumour necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the T cell costimulation inhibitor abatacept, the B cell depleting agent rituximab, and the interleukin 6 receptor (IL-6R)-blocking monoclonal antibody tocilizumab. Adalimumab, certolizumab, etanercept, golimumab and more recently tocilizumab are self-administered as subcutaneous injections, whereas the others are administered by intravenous infusion. Dosing intervals range from every week (etanercept) to a 2-dose course every 6-12 months (rituximab). These differentiating characteristics, as well as patient preferences together with clinical considerations are likely to affect the suitability of any of these medications for individual patients and thus therapy utilization patterns in real-world settings[4]. Besides, mean response rates to biologic therapies in patients with RA are 60% to 70%[5], resulting in a substantial number of patients discontinuing therapy and switching to other biologic or nonbiologic agent. As these are expensive medications, it is important to determine which patients will have an adequate response and for how long[6,7,8].
Some studies have compared drug survival on etanercept, adalimumab and infliximab. Six European studies found that infliximab has shorter survival than adalimumab and/or etanercept initiators, while five other European studies found no differences between drug retention[6,8,9]. A Portuguese study found no significant differences in effectiveness between adalimumab, etanercept and infliximab[10]. Drug survival can be interpreted as a composite measure of effectiveness, safety and tolerability[9].

The evaluation of utilization patterns together with drug survival in a real-world setting would assist clinicians in their choices of biologic therapies.

Study rational

The previously referred studies found different drug retention rates between different biotechnological therapies. We know that patients from different countries present inherent particularities that influence drug preference and also response to therapy, hence we consider highly relevant to perform this type of assessment in a Portuguese population. The ascertainment of the retention rate and retention predicting factors was not performed to date in Portuguese RA patients.

Hypothesis

We hypothesize that RA patients have different drug retention rates and that there are determinants that influence drug retention that should be considered when starting such therapies.

Objectives

This study aims to describe persistence, administration profile, used in clinical practice for the treatment of RA patients.

Primary objective

To assess drug survival of first biotechnological treatment in RA patients registered in Reuma.pt, the Rheumatic Diseases Portuguese Register.

Secondary objectives

To assess the reasons for discontinuing the first biotechnological drug in RA patients (loss of efficacy, adverse event, remission, other) and patterns of switch

To identify predictive factors of the first biotechnological drug discontinuation in RA patients

To assess drug survival and reasons for discontinuation of the second, third and fourth biotechnological drug in RA patients

To perform the same analysis in the subgroup of patients who fulfill the 2010 ACR-EULAR classification criteria for RA

METHODS

Study design

We will perform an observational study including RA patients treated with biotechnological therapies and registered at the Reuma.pt since 2008.

Electronic clinical records will be retrieved for all patients that have been treated for at least 6 months.

Reuma.pt (www.reuma.pt), the Rheumatic Diseases Portuguese Register, became active in 2008 and includes patients with varied rheumatic diseases (rheumatoid arthritis, spondyloathropathies, psoriatic arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, vasculitis and auto-inflammatory syndromes) from the whole country (Portugal mainland, Azores and Madeira islands). Currently 73 public and private rheumatology clinics contribute on a regular basis to the registry.

Eligibility criteria:

- **Inclusion criteria**
  - Patients with RA diagnosis;
  - Patients treated with biological agents registered at Reuma.pt
  - Age ≥ 18 years
  - Having baseline evaluation
- **Exclusion criteria**
  - Diagnosis of other rheumatic diseases

Definitions

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 - first occurrence of any switch to another biological agent within 90 days of the end of treatment of the previous biological.

Temporary discontinuations of < 90 days (which is common for surgery or certain adverse events, for example, infection), after which the patients restarted the same biological agent, are counted as continuous use of the drug.

Variables

Table I. Variables to be collected

Variables to be collected	
Baseline patient characteristics	• Demographic and clinical characteristics (gender, age, education, smoking, alcohol consumption, BMI) • Date of diagnosis of RA • RF and/or ACPA positivity • presence of swollen and tender joints DAS28; HAQ • VAS patient/pain/doctor • CRP; ESR • Comorbidities • presence of systemic features (rheumatoid nodules and secondary Sjögren syndrome) • Previous therapies for RA • Therapy at beginning of biologic
Biological therapy (to be collected for each biological agent used per patient)	• Biological agent • Starting date of treatment • Doses used • Frequency of administration • Therapy during biologic therapy (conventional DMARDs, corticosteroids) • presence of swollen and tender joints • DAS28; HAQ • VAS patient/pain/doctor • Discontinuation date • Reason for discontinuation

- **Primary endpoints**
    - Persistence of first biological therapy (time to discontinuation), by agent, after adjusting for baseline characteristics and other confounders, using clinical data

- **Secondary endpoints**
    - Reasons for discontinuation of biological therapy, by agent and line of therapy, using clinical data, and time to switch of biologic treatment
    - Variables independently associated with discontinuation of biological therapy
    - Persistence of second, third and fourth biological therapy (time to discontinuation), by agent, after adjusting for baseline characteristics and other confounders, using clinical data

ANALYSIS PLAN

Primary aim

Outcomes and their measurements: our primary outcome will be the time to discontinuation of the first biologic. We will use a composite outcome including all causes for discontinuation (no response, loss of response, adverse events, remission or patient willingness). Patients who are loss to follow-up will be censored.
Methods summary: we will report the median drug survival time and the probability of maintaining therapy at prespecified time-points (1 year, 2 years, 5 years and at the end of follow-up time). Time of exposure is from the beginning of therapy with a biotechnological drug to the date of the last administration plus twice the half-life of the biotechnological drug.
The results will be presented graphically as Kaplan-Meier curves and as hazard ratios (HR) and 95% confidence intervals (95%CI). The STATA computer software package will be used to analyze the data collected from this study. Continuous variables will be reported as mean +/- standard deviation (or in case of non-normal distribution as median and quartiles). Nominal variables will be displayed as frequency or proportions.

Secondary aims

As a secondary aim we want to assess the reasons for discontinuation of the first biotechnological drug. Patients will be divided into 5 groups based on reason for discontinuation: nonresponse, loss of response, adverse events, remission, or patient's willingness.
Patients will be classified as responders if they achieve a DAS28 ≤3.2 and DAS28 variation >0.6 at 3 months after the introduction of biological therapy, or >1.2 at 6 months after the introduction of biological therapy. Non-responders will be defined as not achieving this outcome. Secondary failure (loss of response) will be defined as patients classified as responders at week 12 who lose this achievement in two or more evaluations thereafter.

Explanatory variables of discontinuation and their measurements: We will assess baseline clinical and laboratorial predictors of biotechnological treatment discontinuation in RA patients. We will evaluate as our clinical predictor factors: age at beginning of symptoms, time delay between starting symptoms and diagnosis, age at biotechnological drug beginning, disease duration, presence of swollen and tender joints, presence of systemic features, gender, BMI, education level, tobacco and alcohol consumption, disease activity as assessed by baseline DAS28, self-report functional status (disability) measured by the Health Assessment Questionnaire (HAQ), previous conventional DMARD used (methotrexate, leflunomide, sulfasalazine), biotechnological drug used (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab and tocilizumab) and oral corticosteroid therapy. As our laboratorial predictors we will evaluate C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti–citrullinated protein antibodies (ACPAs).

We will use Log rank test to identify which covariates measured at baseline (i.e. previous to biotechnological therapy beginning) associates with biotechnological drug discontinuation on univariable analysis. Variables with p-values smaller than 0.20 will be included in the multivariable analysis. The Cox regression will be used for the multivariable analysis with forward selection method for model building. The final model will include all variables that retain statistical significance ($p<0.05$).

We will perform the same analysis described above for the second, third and fourth biologic, as well as for patients fulfilling the ACR/EULAR 2010 classification criteria for RA.

LIMITATIONS AND EXPECTED RESULTS

We hope to identify the retention rate and predictors of survival of biotechnological therapy in Portuguese patients with RA. These predictors are expected to improve treatment success since they may contribute to adequate treatment choice according to patient and drug specificities.

Limitations include: Possible information bias due to incomplete filling of the database Outcome assessment bias, since patient evaluation and database filling are performed by different rheumatologists from multiple Portuguese centers.

Approximate duration of the study

Timelines for the several steps of this project are presented in Table II. Globally, this study will take 6 - 8 months to be concluded.

Table II. Timeline

	July-Aug	Sep-Oct	Nov-Dec
Data extraction			
Data analysis			
Final report/publication			

Approximate number of participants

Based on the number of patients registered in Reuma.pt with the diagnosis of RA treated with biologics and having baseline information, we expect to include 1300 patients

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.

Results will be presented in an objective way, and will not be hidden or manipulated.

RESEARCH TEAM

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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

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