1. Title:

Safety and effectiveness of biologic Disease-Modifying Antirheumatic Drugs in elderly patients with rheumatoid arthritis

2. Background:

The population of older individuals with rheumatoid arthritis (RA) is expanding, mainly due to increased life expectancy and better health care. The appropriate medical treatment for RA can reduce morbidity and mortality. Treatment options have drastically increased mainly due to development of biologic Disease-Modifying Antirheumatic Drug (bDMARD),that not only improve RA symptoms, but also delay the progression of joint damage, with a reasonable safety profile. Although there is no specific recommendation regarding age as a limiting factor for use of these agents, they are less commonly used in older patients, with a 50% decrease after age 65 compared to patients below age 45 [1]. Most developed world countries have accepted the chronological age of 65 years as definition of 'elderly' or older person (World Health Organization).

Studies have shown that elderly patients with RA may be treated less aggressively than younger patients [2, 3], despite evidence suggesting that biologic treatments may be safe and efficacious in older age groups [4, 5, 6]. However, pharmacokinetic changes associated with aging, particularly decreased renal function and certain types of drug metabolism, may increase the risk for certain adverse drug reactions (7). Clinical studies addressing the safety or efficacy of these medications in this age group are scarce, especially studies evaluating the very elderly (≥75 years). For these reasons we aim to investigate the safety and effectiveness of bDMARDs in older patients with RA.

The Rheumatic Diseases Portuguese Register (Reuma.pt) follows patients with rheumatic diseases under bDMARDs or other therapeutics. Reuma.pt gathers information on patient´s comorbidities, adverse drug reactions as well as disease characteristics and the clinical evolution. As so, Reuma.pt is an excellent tool to evaluate drug safety and efficacy.

Primary objetive:

- To assess the persistence of first bDMARD treatment among elderly patients with RA.

Secondary objetives:

- To assess the persistence of the 1st bDMARD treatment in very elderly RA patients
- To compare the frequency and reasons for the first biologic treatment discontinuation across adults, elderly and very elderly patients;
- To compare the rates of adverse events (serious infections, tumors, allergic reactions) in adults, elderly and very elderly RA patients during the first bDMARD treatment;
- To compare EULAR response and remission in the three groups of patients with RA at 6 and 12 months after initiating a bDMARD;
- To investigate if the choice of first-line bDMARD depends on the patient´s age.

Primary outcome:

- First bDMARD treatment persistence till discontinuation for any reason in RA patients aged 18-64 years versus ≥ 65 years-old.

Secondary outcomes:

- First bDMARD treatment persistence till discontinuation for any reason in RA patients aged 18-64 years versus 65-74 years versus ≥75 years
- Proportion of patients in each age group discontinuing a first bDMARD due to safety, ineffectiveness and other reasons;
- Incidence of AEs (severe infections, opportunistic infections, tumors, cardiovascular events and allergic reactions) across the 3 age groups during bDMARD treatment
- Decrease of DAS28 (ΔDAS), CDAI and SDAI at 6 and 12 months across the three age groups;
- Proportion of patients who achieve EULAR response and remission at 6 months and 12 months;
- Comparison of first bDMARD choice across the three age groups.

Methodology

Prospective multicenter observational cohort-study of patients with diagnosis of RA and treated with a first bDMARD, using data from the Reuma.pt database.

Inclusion criteria: Patients with RA diagnosis registered in the Reuma.pt database starting a first bDMARD.

Exclusion criteria: RA patients with <18 years old; patients in clinical trials; patients with other connective tissue diseases, except secondary Sjogren's syndrome

Variables at baseline (date of first bDMARD initiation):

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

• Age of first symptoms;

• Age and calendar year of RA diagnosis;

• RA characteristics: Rheumatoid factor and/or ACPA positivity, erosive disease, number of swollen and tender joints, ESR, CRP, Patient and Physician global assessment of disease activity (VAS), Pain (VAS), DAS28 4V, CDAI, SDAI, HAQ-DI);

• Comorbidities (hypertension, dyslipidemia, cardiovascular diseases, diabetes, renal insufficiency, osteoporosis, previous infections, previous neoplasia)

• Time from diagnosis to 1st bDMARD:

- Start date of bDMARD initiation;

• Concomitant medication: current use and dose of corticosteroids and conventional synthetic DMARDs (csDMARDs); number of previous csDMARDs.

At follow up (6 months, 12 months, last observation or bDMARD discontinuation):

• Tender and swollen joint count, ESR, CRP, DAS28 4v, CDI, SDAI, HAQ at 6months and 12months of bDMARD therapy;

• Discontinuation date and reason for discontinuation;

• AEs throughout the treatment.

. Time since beginning of bDMARD therapy till occurrence of AE.

Comparison of bDMARD choice across the two age groups will be performer only in patients starting bDMARD after 2009 (time when most bDMARDs were available).

Definitions:

- Population age groups: Adults - 18 to 64 years-old; Elderly - ≥ 65 years-old; Very elderly - ≥ 75 years-old
- Remission: DAS28 <2.6; CDAI ≤2.8; SDAI ≤3.3
- Discontinuation is defined as either one of the following events:
    - End of treatment registered by the treating physician (regardless of the reason)
    - Switch to a different bDMARD
    - 90-day continuous gap of treatment without a posterior bDMARD treatment, except for 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.
- Reasons of discontinuation: AE, ineffectiveness and other (includes remission, patient willingness, pregnancy planning and unknown).
- Adverse events will be categorized as: infections, tumors, allergic reactions and cardiovascular events. AE might be detailed according to the available information
- Previous infections: documentation of HIV, hepatitis B, hepatitis C or tuberculosis before 1st bDMARD administration.

Statistical analysis:

Descriptive analysis of continuous variables will be reported as mean and standard deviation, or median and interquartile ranges for variables with skewed distribution. Descriptive analysis of categorical variables will be presented as frequencies and percentages.

Baseline data will be compared between the three groups (<65years, 65-74 years and ≥75 years) using the chi-square test for categorical variables and ANOVA (or K-W test) for continuous variables.

Follow-up time will be calculated as time in months from initiation of 1st bDMARD until discontinuation because of AE. Kaplan-Meyer will be used to calculate persistence rate in biologic treatment.

Reasons for discontinuing therapy will be summarize using descriptive statistics and stratified by the patient´s age (<65years, 65-74 years and ≥75 years).

The safety analysis will be performed by calculating the cumulative incidence of adverse events according to patient age group (all adverse events, serious adverse events and adverse events that led to bDMARD discontinuation).

Raw and adjusted comparisons of disease activity, EULAR response and remission, after 6 and 12 months of treatment, will be performed. For correction to attrition bias we will use Lundex index.

P- value will be considered significant at <0.05.

Expected results:

With this study we expect to characterize the safety and effectiveness of bDMARDs in the elderly RA patients, a population frequently excluded from clinical trials.

Limitation of the study

Since registration in Reuma.pt database is voluntary, it is possible that some information is incomplete, especially regarding the occurrence of adverse reactions. All participating centers will be invited to complete data, whenever possible.

Calendar:

Data extraction and database cleraning: November-December 2018

Data analysis: January-February 2019

Final report: March 2019

Research team:

- Proponent: Raquel Freitas - Rheumatology department Hospital Garcia de Orta

- Research team: Monica Eusébio – Portugueses Society of Rheumatology - Fátima Godinho, Maria José Santos - Rheumatology department Hospital Garcia de Orta

Role of research team members:

Raquel Freitas: study concept and protocol development, database management, statistical analysis, interpretation of results, preparation and revision of communications and scientific publications
Monica Eusébio: protocol development, database management, statistical analysis, interpretation of results, preparation and revision of communications and scientific publications

Fatima Godinho: study design, interpretation of results, preparation and revision of communications and scientific publications
Maria José Santos: study concept and protocol development, interpretation of results, preparation and revision of communications and scientific publications

- 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 rules up to a maximum of 2 per center.

Ethical consideration:

The study will be conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) and will be submitted for evaluation and approval to the Ethics Committee of Hospital Garcia de Orta.

Conflict of interest: There is no conflict of interest.

Funding: There is no funding

References:

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