Protocol

1. Title: Biologic Disease-Modifying Antirheumatic Drugs survival and safety in Late-onset axial Spondyloarthritis – data from a Portuguese Registry

2. Abstract:

Rationale: Axial spondyloarthritis (axSpA) symptoms usually begin before 45 years old, but due to longer duration of life expectancy and improved health services, late-onset axSpA (Lo-axSpA) is being more recognized. Previous studies have shown different clinical characteristics, however data regarding safety or efficacy of biological Disease-Modifying Drugs (bDMARDs) in Lo-axSpA are scarce and it seems important to us to understand if bDMARD efficacy is influenced by Lo-axSpA, or by the age of treatment onset.

Aim: To evaluate drug survival and safety of bDMARDs treatment in Lo-axSpA patients in comparison to those with early-axSpA (E-axSpA).

Methods: Retrospective multicentre national cohort study, with patients with a diagnose of axSpA, registered in Reuma.pt, the Portuguese registry of patients with rheumatic and musculoskeletal diseases.

Analysis plan: Patients will be divided into 2 groups based on their age at symptom onset: E-axSpA (age <45 years); and Lo-axSpA (age ≥45 years), accordingly to the Assessment of Spondyloarthritis International Society (ASAS) classification criteria. Generalized linear mixed models will be used to evaluate the group differences in BASDAI, ASDAS-CRP and ASDAS-ESR, and BASFI. Drug survival will be calculated as time in months from initiation of bDMARD until discontinuation/switch. Log-rank test will be used to calculate persistence rate in biologic treatment.

Expected results: We expect to evaluate the response to bDMARDs in Lo-axSpA patients to understand if it is a different entity, with the need of a customized management.

Ethics: The study will be conducted according to the principles of the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies.

3. Rationale:

Spondyloarthritis (SpA) is a group of heterogeneous inflammatory rheumatic diseases. Axial spondyloarthritis (axSpA) is the prototype of this group and is characterized by typical axial involvement with imagological evidence of sacroiliitis[1]. Usually, symptoms begin before 45 years old. However, due to longer duration of life expectancy and improved health services, late-onset axSpA (Lo-axSpA) is being more recognized.[2]

There is no definition for Lo-axSpA, and the cut-off varied significantly across studies, making difficult to compare them and to set a cut-off.[3] It is estimated that the prevalence of Lo-SpA is up to 11%.[4] The diagnosis of Lo-SpA may be challenging, since the entry criteria of the Assessment of Spondyloarthritis International Society (ASAS) classification criteria is inflammatory back pain starting and <45 years old.[5] Compared with patients with early-onset Spondyloarthritis, patients with Lo-axSpA seem to have more cervical and shoulder involvement, a higher elevation of laboratory parameters of inflammation and a lower proportion of hip involvement.[6,7,8] A Brazilian cohort with 1424 patients with SpA showed that patients with disease onset after 40 years old were more females and had more peripheral arthritis.[4]

Biologic Disease-Modifying Antirheumatic Drugs (bDMARDs) are important treatment options in patients with inflammatory arthritis. However, not all patients respond to these therapies, and the ability to identify these patients may help to minimise the risks and costs associated with these treatments. Younger age has been shown as a good predictor of response to Tumour Necrosis Factor (TNF) antagonists.[9] On the other hand, other studies have shown no differences between younger and older patients in axSpA.[10,11] Data regarding bDMARDs efficacy in patients with Lo-axSpA is limited. A recent Korean study reported a lower efficacy and drug retention in patients with Lo-axSpA.[12] Thus, it seems important to us to understand if bDMARD efficacy is influenced by Lo-axSpA, or by the age of treatment onset.

3. Aims: The purpose of this study is to evaluate drug survival and safety of bDMARDs treatment in Lo-axSpA patients in comparison to those with E-axSpA.

3.1. Primary outcome:

- To compare bDMARD drug discontinuation/switch rates, and their reasons, between patients with Lo-axSpA and E-axSpA.

3.2. Secondary outcomes:

- To compare the rates of adverse events.

- To compare the difference (Δ) in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis

Functional Index (BASFI) between baseline and 6 months and between baseline and 12 months after initiation of bDMARD.

- To compare BASDAI, ASDAS and ASAS response and remission in the two groups at 6 and 12 months after initiation of bDMARD.

4. Type of study

Retrospective multicentre national cohort study.

5. Data source and study population:

The present study will be performed using secondary data from patients with the diagnosis of axSpA registered in the Rheumatic Diseases Portuguese Register (Reuma.pt).

5.1. Inclusion criteria:

- Patients registered in the Reuma.pt
- Patients with axSpA diagnosed by their treating Rheumatologist
- Age of symptom onset of ≥18 years old
- bDMARD naïve-patients

5.2. Exclusion criteria:

- Patients with other inflammatory rheumatic diseases

5.3. Variables and Time Points to be collected:

- **Variables at baseline (date of bDMARD initiation):**

- Socio-demographic and clinical characteristics: gender (male or female), age (years), years of formal education (0-4, 4-6, 6-9, 9-12, >12), smoking status (current smoker or no current smoker), alcohol consumption (no-consumption or current consumption), body mass index (kg/m2), working status

- Age of first symptoms (years)

- Age at diagnosis (years)

- Age at beginning of bDMARD (years)

- SpA characteristics: HLA-B27 positivity (yes or no); family history of SpA (yes or no); dactylitis (yes or no); enthesitis (yes or no); uveitis (yes or no); bowel inflammatory disease (yes or no); psoriasis (yes or no); preceding infection (yes or no), inflammatory bowel disease (yes or no), peripheral arthritis (yes or no)

- Imaging: sacroiliitis on radiographs (according to modified New York criteria) or magnetic resonance imaging (yes/no)

- Disease activity: ESR (mm/h); CRP (mg/dL); Patient and Physician global assessment of disease activity (VAS; 0-100), Pain (VAS; 0-100), ASDAS, BASDAI, BASFI, ASAS 20 and 40, Bath Ankylosing Spondylitis Metrological Index (BASMI).

- Comorbidities: Hypertension (yes or no), dyslipidaemia (yes or no), cardiovascular diseases (yes or no), diabetes (yes or no), renal insufficiency (yes or no), osteoporosis (yes or no), previous neoplasia (yes or no), demyelinating diseases (yes or no)

- bDMARD or tsDMARDs initiated (anti-TNF, IL17i, IL12/23i, tofacitinib)

- Concomitant medication (yes or no): non-steroidal anti-inflammatory (NSAIDs), conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARD), corticosteroids.

6.2. At follow-up (3 months, 6 months, 12 months and bDMARD discontinuation/last observation):

- ESR; CRP; Patient and Physician global assessment of disease activity (VAS; 0-100), Pain (VAS; 0-100), ASDAS-CRP and ASDAS-ESR, ASAS 20 and 40, BASDAI, BASFI, ASAS20 and ASAS40.

- Discontinuation/switch date and its reason: adverse events, inefficacy (primary and secondary failure), remission, others (patient preference, change in hospital, pregnancy).

- Adverse events throughout the treatment.

6.3. Definitions:

- Treatment response based on disease activity will be evaluated using ASDAS - response criteria (ASDAS clinically important and major improvement: defined as a decrease from baseline of ≥ 1.1 and ≥ 2.0 units, respectively) and BASDAI50.

- Primary and secondary failures are defined according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) clinically important improvement (Δ ≥1.1 as compared to baseline): a patient will be classified as primary failure if a response at 3 or 6 months is not achieved and secondary failure if a response is achieved at 3 or 6 months and then lost any time during the follow-up.

6.4. Analysis plan:

Patients will be divided into 2 groups based on their age at symptom onset: Ao-axSpA (age <45 years); and Lo-axSpA (age ≥45 years), accordingly to the ASAS classification criteria.

Descriptive analysis of continuous variables will be reported as mean and standard deviation, or median and interquartile ranges, if normal or skewed distribution, respectively. Categorical variables will be presented as frequencies and percentages.

Baseline data will be compared between the two groups, using the chi-square test for categorical variables and t-student (or Mann-Whitney) for continuous variables.

To evaluate the group differences in BASDAI, ASDAS-CRP and ASDAS-ESR, and BASFI longitudinal data outcomes will used generalized linear mixed models (GLMM).

Drug survival will be calculated as time in months from initiation of bDMARD until discontinuation/switch. Log-rank test will be used to calculate persistence rate in biologic treatment. The results will be presented graphically as Kaplan-Meier curves and as hazard ratios (HR) and 95% confidence intervals (95%CI). A logistic regression will also be used to build a prediction model of drug retention and we will analyse its power of discrimination using ROC curves.

Cumulative incidence of adverse events will be calculated according to patient age group (all adverse events, serious adverse events and adverse events that led to bDMARD discontinuation).

The data will be analysed using R software version 4.1.1. P-value will be considered significant at ≤0.05.

7. Expected results and limitations:

Expected results:

With this study we expect to evaluate the efficacy and drug retention rate of bDMARDs in Lo-axSpA patients.

Limitations:

Since it is estimated that Lo-axSpA has a low incidence, we might have a small number of patients. The research team asked for information about the number of patients registered in the Reuma.pt database: 4178 patients, of which 439 patients had initial axSpA symptoms after 45 years old.

Missing values will be overcome completing prospectively data, using clinical records. All participating centres will be invited to complete data, whenever possible. If not possible, to take advantage of all available data it will be used specific procedures as generalized estimating equations (GEE). In the presence of missing data, imputation techniques will be applied to perform sensitivity analysis on the results.

8. Timeline:

Task 1 - Project submission to Reuma.pt scientific commission (CCC): January – June 2022

Task 2 - Data extraction: July - August of 2022

Task 3 – Data prospectively completed: September and October of 2022

Task 4 - Data analysis: November of 2022

Task 5 - Manuscript and abstract writing: December of 2022

Task 6 – Abstract submission to EULAR 2023 and Portuguese Rheumatology Congress 2023.

Task 7 – Manuscript submission: January 2023

9. Research Team:

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9.1. Institution involved: participation is open to all Portuguese centres interested in collaborating in this project. Authorship will follow the International Committee of Medical Journal Editors and Reuma.pt rules.

10. Ethics:

Data will be anonymous, and no patient identifiable information will be captured. All patients had previously given and informed consent for clinical purpose and research before they were included in the database.

The study will be conducted according to the principles of the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies.

It will be submitted for evaluation and approval to the Ethics Committee of Centro Hospitalar Baixo Vouga and to the Coordinator and Scientific Board of Reuma.pt.

11. Funding and conflict of interests: There is no funding nor conflict of interest.

12. References:

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