TITLE

Long-term predictors of quality of life in axial Spondyloarhritis

BACKGROUND

Spondyloarthritis is a chronic inflammatory rheumatic disease involving the axial skeleton (spine and sacroiliac joints), enthesis and peripheral joints, and may occur together with extra-articular manifestations, such as uveitis, psoriasis and inflammatory bowel disease.[1] According to the cardinal manifestations of the disease, the Assessment of SpondyloArthritis international Society (ASAS) developed classification criteria for axial Spondyloarthritis (cardinal manifestation: back pain)[2] and peripheral Spondyloarthritis (cardinal manifestations: arthritis, enthesitis or dactylitis)[3]. Axial Spondyloarthritis (axSpA) is characterized by inflammation and bone formation in the spine (syndesmophytes) and sacroiliac joints. This entity includes patients with radiographic changes defined on sacroiliac joints (radiographic axSpA), whose hallmark is Ankylosing Spondylitis, and those without, but with typical changes in magnetic resonance imaging (non-radiographic axSpA).[2,4]

There is a rough correlation between the presence of human leukocyte antigen B27 (HLA-B27) and the incidence and prevalence of this disease in a specific population. Overall, the prevalence of ankylosing spondylitis is between 0,1% and 1,4%, with most of these data coming from Europe.[4] In Portugal it was estimated 1.6% for Spondyloarthritis and 0.5% for Ankylosing Spondylitis, data from EpiReumaPt, the largest epidemiological study in our country.[5]

Spondyloarthritis affects mainly young adults, in the 3rd and 4th decades of life[6], being chronic back pain, stiffness and fatigue the main symptoms[4] and loss of spinal mobility, due to spinal inflammation, structural damage or both, a major concern.[7]

It is becoming increasingly important to evaluate the overall impact of the disease and the general state of patients with axial Spondyloarthritis. During the process of the disease, complaints like pain, fatigue and limited mobility, have repercussions on different aspects of the patient's life, such as their psychological state, occupational productivity[8], and quality of life (QoL).[9]

Health-related QoL has been increasingly recognized as both an important indicator of the burden of Ankylosing Spondylitis and a highly relevant outcome in this disease treatment. A meta-analysis of 38 studies revealed that generic health-related QoL was significantly lower in patients with Ankylosing Spondylitis compared with the general population.[10] Impairment of QoL seems to be mainly associated with disease activity[11] (related to inflammation) and worsening of functionality.[12] It is also well known that sleep problems, depression, and sexual disfunction are also important manifestations of the disease with a great impact on QoL.[12] Indeed, axSpA patients seem to have higher levels of psychological distress and a recent systematic review and meta-analysis confirms the increased risk of anxiety and depression among patients with Ankylosing Spondylitis.[13]

As it was mentioned above, axSpA has its onset in the most productive ages of life, thus, function impairment and activity limitations can have important socio-economic consequences because they affect people who have just start working. The work participation of axial Spondyloarthritis patients with a longstanding disease has previously been reported in several studies, which showed a correlation between decreased work productivity and increased disease-related sick leave[14–16] Still, there are very few data on the effect of specific aspects of work and its influence on axSpA, either we consider disease activity or structural progression. Regarding disease activity, a prospective study, with a 3-year follow-up, DEvenir des Spondyloarthrites Indifférenciées Récents (DESIR), examined disease trajectories and factors associated with them. In this study "persistent inactive disease" was strongly associated with "white-collar jobs" (less physical demanding)[17]. Considering structural progression, *Ramiro et al.* [18] reported in a longitudinal analysis of 136 patients that the relationship between disease activity and radiographic progression was significantly and independently modified by job-type, with "blue-collar workers" (more physical demanding) presenting more structural progression of the disease. The authors hypothesized that physically demanding jobs amplify the potentiating effects of inflammation on bone formation in Ankylosing Spondylitis. However, these results may reflect confounding, as job-categories are very closely linked to income and socio-economic status and even smoking status (which is already known to be closely related to disease activity and radiographic progression[1]).

Management of axSpA should aim at the best possible health-related QoL.[19] As an inflammatory disease, suppression of inflammation by drugs is a key approach to the treatment in order to relieve symptoms, preserve physical function and maintain QoL. And indeed, data have accrued that suggest a direct relationship between clinical disease activity and syndesmophyte formation and between disease activity and function.[19] Moreover, patients who have inactive disease have better QoL.[11] Treatment should be individualized according to current clinical manifestations (axial, peripheral, extra-articular) and patients' characteristics including comorbidities and psychosocial factors. Beyond non-pharmacological interventions (exercise, stop smoking, physical therapy), patients suffering from pain and stiffness should use non-steroidal anti-inflammatory drugs (NSAIDs) as first-line drug treatment but biological therapy should be considered in patients with persistently high disease activity despite conventional treatments.[19] A comprehensive review from *Kotsis et al*[20] supports that pharmacological treatment along with physical exercise can minimize the effects of axSpA in QoL.

In sum, axSpA is an inflammatory rheumatic disease that often causes severe disability and impaired QoL. Disease activity is one of the most powerful predictors of QoL, however, advances in drug treatment have minimized this impact. Along with disease activity many other factors seem to be determinant for QoL and some of those factors have been more studied than others. Recent data suggests occupational activity may be one of those factors as it influences structural disease progression (syndesmophyte formation) and

QoL in patients with axSpA but very scarce data is available on the influence of occupational activity in long-term response to therapy and QoL.

In this project, we propose to evaluated real-world long-term determinants for QoL in axSpA patients, with special focus on socio-economic status, occupational activity, work outcomes, psychological profile, disease activity, function and therapy (conventional *versus* biological). We hypothesize that occupational activity influences long-term QoL and response to treatment and as such, patients with more physical demanding occupational activities, which are associated with more mechanical strain to the enthesis, have worse long-term QoL and lower response to treatment.

OBJECTIVES

Primary objective

- To identify long-term predictors of QoL in axSpA.

Secondary Objectives

- To evaluate the influence of socio-economic status, occupational activity, and biological therapy in long-term QoL, in patients with axial Spondyloarthritis.
- To compare work outcomes and long-term QoL in patients with axial Spondyloarhritis on biological therapy with those on conventional treatment.
- To determine the cost-utility of biological therapy in axial Spondyloarhritis
- To analyze the influence of socio-economic status and occupational activity, in long-term response to treatment, regarding disease activity and function, in patients with axial Spondyloarthritis.
- To identify determinant factors for treatment decision (biological *versus* non-biological) beyond disease activity, in axial Spondyloarhritis.

METHODOLOGY

Study design

Prospective cohort multicentre study of patients with diagnosis of axSpA using real world anonymous patient-level data from the national register database Reuma.pt.

Using the nationwide database of Reuma.pt will allow real-world anonymous patient-level data analysis. Data will be retrieved for all patients who fulfill the study's eligibility criteria, as detailed bellow. Thus, data will be anonymous and no patient identifiable information will be captured. All results will reflect the treatment, procedures and diagnostic methods according with the physicians' routine clinical practice.

Inclusion criteria

Patients with the diagnosis of axSpA with 3 or more years of follow-up in Reuma.pt.

Exclusion criteria

We will exclude patients with the diagnosis of peripheral spondyloarthritis

Study Variables

Data will be collected regarding sociodemographic data (year of birth, gender, BMI, education degree, profession, working status) and lifestyle characteristics (alcohol intake and smoking habits, frequency, and type of physical activity). Physical activity will be evaluated by a self-reported questionnaire, the International Physical Activity Questionnaire (IPAQ), that will be administered and added to the database for the purpose of this research project. Information regarding employment status is collected when patients' data is introduced in the database (full-time, part-time, unemployed, retired, working at home, sick leave for more than 1 month) and usually are not updated. To have more accurate information about employment status some additional data will be collected through a specific questionnaire, the Work Productivity and Activity Impairment questionnaire (WPAI), that also needs to be included in the database for the purpose of this research project. Besides disease characterization (date of first symptoms, date of Spondyloarthritis diagnosis, patient's extra-articular manifestations related to the disease like uveitis, psoriasis and inflammatory bowel disease, HLA-B27), we will also assess:

- patient's and physician's Visual Analogue Scale (pVAS; phVAS);
- disease activity: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (ASDAS-CRP);
- enthesis involvement by the Maastricht Ankylosing Spondylitis Enthesis Score (MASES);
- disease function: Bath Ankylosing Spondylitis Disease Function Index (BASFI), HAQ, SF-36;
- QoL by Ankylosing Spondylitis Quality of Life (ASQoL) and Euro Quality-of-Life – 5 dimensions (EQ-5D);
- fatigue by Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT F);
- anxiety and depression by HADS;
- Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), with the respective units, per standard of care;
- therapy: biological therapy, conventional Disease-Modifying Anti-Rheumatic Drugs (DMARDs), corticosteroids, NSAIDs;
- comorbidities (arterial hypertension, diabetes mellitus, dyslipidemia, renal insufficiency, pulmonary involvement)

These variables will be collected at baseline and after 1 and 3 years of follow-up.

Regarding occupation activity (job) it will be classified according to the physical demand on the job. Two groups of patients will be considered: "blue-collar workers", for those with more physically demanding jobs and "white-collar workers" for those with less physically demanding jobs. Up to now, there are no

published criteria to classify jobs into these two categories and in all published work using this methodology, classification was made according to the investigator's criteria.

Disease activity response will be evaluated by ASDAS-CRP response criteria (ASDAS clinically important and major improvement: ≥1.1 and ≥2.0 improvement, respectively).

To evaluate determinants for treatment decision we will analyze the following variables: age, sex, education degree, job-type, pVAS, phVAS, function, enthesis involvement, fatigue, anxiety, depression, extra-articular manifestations of the disease, comorbidities, and variables more closely related to systemic inflammation (CPR, ASDAS-CRP).

To evaluate the cost-utility of biological therapy we will consider therapy costs, EQ-5D, presenteeism, and sick leave in the last year of follow-up.

Statistical analysis

Statistical analysis will be performed considering the three groups of patients: spondyloarthritis, low back pain, and participants with no rheumatic disease.

Absolute frequencies and weighted proportions will be used to summarize categorical variables. Continuous variables will be described by weighted mean values and standard deviations (for normal distribution) or median and interquartile ranges for variables with skewed distribution.

Univariate and multivariate regression models will be performed to assess relations between QoL (AsQoL and EQ-5D) and sociodemographic data (age, gender, BMI, education degree, job-type), lifestyle habits (smoking, alcohol, exercise), fatigue, depression, anxiety, comorbidities, type of therapy and disease-specific variables (enthesis, function, activity: CRP, ESR, ASDAS-CRP, BASDAI).

The 1-year and 3-year persistence rates, together with corresponding 95% CI, will be estimated based on the time to biologic discontinuation curve (i.e. biologic survival curve) using the Kaplan-Meier (KM) method.

EXPECTED RESULTS AND STUDY LIMITATIONS

We also expect to determine long-term predictors for QoL in axial Spondyloarhritis and to demonstrate that patients on biological therapy have better QoL than patients on conventional treatment. Specifically, we hope to understand the influence of occupational activity in disease activity, function, treatment response, and ultimately, in QoL. We believe that patients with more physically demanding jobs have worse QoL and lower response to therapy.

Drug therapy is one of the cornerstones of axial Spondyloarhritis management and we expect to identify other factors beyond disease activity (sex, education degree, psychological profile, comorbidities) that influence physicians' therapeutic decisions. As axial Spondyloarhritis has a high impact on work

outcomes, that can be modified by therapy, we also expect to demonstrate long-term impact in work outcomes and the cost-utility of biological therapy.

Further knowledge into real-world determinants for QoL in axial Spondyloarthritis can have important repercussions in the management of these patients. Furthermore, if we confirm our hypothesis, job-type and education level may become relevant, when a therapeutic decision is being considered and allowing to select patients more prone to respond to expensive therapies, as expenses with biological therapy are a matter of major concern all over the world.

Limitations such as underreporting and missing data are expected. In order to minimize missing data, all participating centres will be asked to complete the dataset with information from the medical charts, when available. Data on physical activity will only be collect once the project starts and there will be no retrospective data but we believe that for the majority of patients will translate usual exercise practice.

TIMELINE

Timelines for the several steps of this project are presented in the table below. Globally, it is estimated that it will take 3 years to be concluded.

Task description	2020		2021				2022				2023			
	Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec
Protocol submission and approval														
Inclusion IPAQ and WPAI in Reuma.pt														
Reuma.pt centers recruitment														
Data collection of IPAQ and WPAI														
Data extraction and cleaning														
Data analysis														
Dissemination of results														
Manuscript writing														
Manuscript Review														
Manuscript Publication														

RESEARCH TEAM

Proponents

Helena Santos – Instituto Português de Reumatologia; Fernando Pimentel dos Santos – Rheumatology Department Centro Hospitalar Lisboa Oriental; Helena Canhão – Centro Hospitalar Lisboa Central.

Institutions

The project is open to all national rheumatology centres interested in cooperating.

ETHICAL CONSIDERATIONS

This study will be conducted according to the Declaration on Helsinki (revised in Fortaleza – 2013) and will be submitted for evaluation and approval to the Ethics Committee of Instituto Português de Reumatologia.

CONFLICT OF INTEREST AND FUNDING

This project has not received any financial support.

There is no conflict of interest from the proponents.

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