**Formulário de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da SPR**

**Title:** Adult outcomes of Juvenile Idiopathic Arthritis

**Background:**

The global burden of Juvenile Idiopathic Arthritis (JIA) is not accurately established. Inconsistencies of classification and on evaluation of disease activity and disability in addition to loss to follow-up, frequently due to change of medical care from pediatric into adult rheumatology, have contributed to incomplete understanding of the impact of JIA in adult age. When JIA patients reach adulthood they have frequently their diagnosis freely reclassified using adult rheumatic diseases terminology. However, apart from our previous work [1], there is no published data on how adult JIA patients fulfill classification criteria for adult rheumatic diseases and the available information, especially in the post biologic treatments era, on functional status, quality of life, comorbidity and irreversible damage of adults that were affected by these childhood onset diseases is very scarce. Thus, understanding the long-term clinical course of JIA, especially in the biologic era, is a relevant unmet medical need.

Our hypothesis is that the long-term outcomes of JIA patients are at least as severe as those of adult onset rheumatic diseases and that clinical variables and the use of biologic treatments influence JIA outcomes.

**Objectives:**

Our main objective is to determine how long-term outcomes of JIA compare with adult onset counterpart rheumatic patients, to identify predictors of poor outcome and the impact of biologic treatment on the outcomes evaluated.

The specific objectives are:

1. To compare the quality of life, function, fatigue, anxiety and depression in adult JIA patients and adult onset counterpart rheumatic patients.
2. To compare irreversible damage in adult JIA patients and adult onset counterpart rheumatic patients.
3. To determine clinical predictors of poor outcome in JIA
4. To assess the influence of biologic treatment on JIA outcomes.

**Methods:**

This is a cohort study using data from Rheumatic Diseases Portuguese Register (Reuma.pt) complemented with additional data accessed by direct interview of a subset of patients selected from Reuma.pt.

**Study population:**

Inclusion criteria: patients with JIA according to the 2001 revised International League of Associations for Rheumatology (ILAR) criteria, registered in Reuma.pt, that at the time of data analysis are older than 18 years old, had a disease duration greater than 5 years and have available data in adulthood. In the Reuma.pt JIA protocol there is a field asking the physician to check if the adult JIA patient fulfills classification criteria for any of the following adult rheumatic diseases: Rheumatoid Arthritis (RA); Spondyloarthritis (SpA); Psoriatic Arthritis (PsA); adult Still disease (ASD); non-classifiable. Data registered in this Reuma.pt field will be analysed in order to allow comparison with a control group of patients with adult onset rheumatic diseases. The comparator group will be constituted by patients with adult onset rheumatic diseases (RA, SpA, PsA, ASD) registered in Reuma.pt, matched for sex and disease duration.

**Expected sample size**

There are currently more than 1700 JIA patients registered in Reuma.pt. Of those, 740 are adults and potentially eligible for the first objective. For the other objectives, admitting the possibility that a relatively large proportion of these patients will not be willing to participate, due to time consuming issues involved in a medical visit and imaging exams, we estimate a sample of 200 adult patients with JIA.

The comparator group, will be constituted by the same number of patients, with adult onset rheumatic diseases (RA, SpA, PsA, ASD) registered in Reuma.pt, matched for sex and disease duration.

**Study plan:**

<u>Task 1: Patient selection</u>

First step: Selection of JIA patients as defined in the description of the study population.

Second step: Selection of matching patients with adult onset rheumatic diseases as defined in the description of the study population.

Third step: Invitation for on-line, post or phone response to questionnaires to achieve objective one.

Fourth step: Invitation for an appointment, made concomitantly with the third step, to achieve objectives two, three and four.

Task 2: Quality of life, function, fatigue, anxiety and depression

Patients selected in task 1 will be invited to fill in the following questionnaires, in Reuma.pt, preferentially online, but if needed due to cultural or educational barriers the questionnaire will be applied by post or by phone and then registered in Reuma.pt: Medical Outcomes Study 36-item Short Form (SF-36[2]), Health Assessment Questionnaire - Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F, [3]) and Hospital Anxiety and Depression Score (HADS, [4]). SF-36 will be used as a measure of generic health status and quality of life as assessed in its eight domains, with scores ranging from 0 (worst) to 100 (best) for each domain. Functional disability will be measured by HAQ-DI. FACIT-F Scale Scores range from 0 to 52, with higher scores indicating less fatigue. HADS is comprised of 7 items each for assessing clinically significant anxiety.

Task 3: Irreversible damage

Patients selected in task 1 will be invited for an appointment and additional evaluations.

Extra-articular damage will be assessed by Juvenile Arthritis Damage Index- Extra-articular (JADI-E, [5]). We will also collect information on comorbidities of special interest (ischemic cardiovascular disease, cerebrovascular disease, chronic lung disease, neurological disease, chronic renal and liver impairment, gastrointestinal disease [inflammatory bowel disease, diverticulitis, ulcers] diabetes, thyroid disease and cancer).

For the evaluation of joint damage, radiographic assessment of affected joints (adapted to the JIA category) will be requested. Joint damage will be scored by the Juvenile Arthritis Damage Index-Articular (JADI-A, [5]) and for JIA patients that could be currently classified as RA and for adult onset RA control group, by an adapted version of the Sharp/van der Heijde score, [12]. Bone mineral contents measurement will be performed at the lumbar spine and the proximal femur by dual-energy X-ray absorptiometry (DXA) in Hospital Santa Maria. Bone mineral density (BMD) will be expressed in $g/cm^2$ and in T-scores. Normative values provided by Lunar Prodigy will be used for the determination of T-scores.

Task 4 – Predictors of JIA outcome

The following covariables will be retrieved from Reuma.pt and analysed as potential predictors of outcome: gender, ethnicity, age at disease onset, years of education, employment status (employed, unemployed, retired and retired due to JIA induced disability), ILAR category at onset, disease duration (years), presence of rheumatoid factor, anti–citrullinated

protein antibodies, antinuclear antibodies and HLA B27, disease activity, current and previous therapy with corticosteroids, disease modifying antirheumatic drugs and biological therapy.
Disease activity will be assessed and patients classified as having active or inactive disease. For that, the number of swollen/tender joints, patient and physician's global assessment of disease activity (0-10), back pain (0-10), morning stiffness intensity (0-10), erythrocyte sedimentation rate (ESR, mm/first hour) and C-reactive protein level (CRP, mg/dl) and extra-articular manifestations will be assessed. Disease activity will be assessed through disease specific activity indexes according to the adult rheumatic disease: Disease Activity Score (DAS) 28 for patients classified as RA, DAS 44 for PsA and peripheral SpA patients, and *AS Disease Activity Score (*ASDAS) for axial SpA. Patients will be classified as having inactive disease based on cut-offs defined for each index: DAS 28 < 2.6, [8]; DAS 44 <1.6, [9]; ASDAS <1.3, [10]. Patients classified as ASD or with non-classifiable adult rheumatic disease, will be considered to have inactive disease if they have: no active arthritis; no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR and/or CRP; a physician's global assessment of disease activity rated at the best score possible [10].

Task 5 – The impact of biologic treatment on JIA outcome

For all patients selected in task 1 detailed data on the use of biologics will be collected from Reuma.pt and if needed additional information will be obtained from the appointment with patients and from the participating centres.

Task 6- Data analyses

Categorical variables will be described using absolute and relative frequencies. Percentages are based on the total number of subjects with non-missing values unless specified otherwise. Missing values will not be considered in the percentages. For continuous data mean, standard deviation, median, $25^{th}$ and $75^{th}$ percentiles, minimum, and maximum and number of non-missing, will be calculated. Whenever necessary (due to small numbers or zero counts), categorical variables will be re-categorized collapsing original categories (or consecutive categories in case of ordinal data). Continuous variable can be categorized whenever the grouping makes sense for separate group risk analysis or when a very small of discrete values is observed.
A descriptive analysis of the quality of life, function, fatigue, anxiety and depression, structural damage and comorbidities present in the whole group of adult JIA patients will be performed and compared with results from adult onset counterpart rheumatic patients. Subsequently patients will be grouped according to the adult diagnosis and the analysis

repeated. The score of an adapted version of the Sharp/van der Heijde will be compared between JIA patients that could be currently classified as RA and adult onset RA. With the purpose of find differences in median scores of the patient reported outcomes and in the severity of damage in adult JIA patients when compared with adult onset counterpart rheumatic patients, univariate analysis will be performed to assess the possibility of confounders. We will use multivariate linear regression models in order to adjust for the differences between the groups.

We will determine clinical predictors of poor outcome in JIA based on clinical and laboratorial data listed in task 4. We will consider outcome variables quality of life, function, fatigue, anxiety, depression and irreversible damage. Possible associations between covariables and patient reported outcomes will be evaluated using uni and multivariate linear regression. The potential associations between putative disease-related risk factors and BMD at both the spine and hip, and JADI scores will be studied by uni and multivariable linear regression for continuous response variables and logistic regression for binary response variables.

In order to find the effect of biologic treatment, JIA patients will be grouped according to disease onset before or after the year 2000, when biologics became available in clinical practice. Additionally, we will also compare outcomes between patients not treated with biologics, with those in whom biologic treatment was started less than 2 years, between 2-5 years or more than 5 years after JIA onset, by ascertain for possible confounders, followed by multivariate linear regression models.

In all analyses significance level will be set at 0.05. All analyses will be performed using Stata IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

**Expected results and possible limitations:**

We expect to determine the long-term outcomes of JIA and to identify predictors of poor outcome and the impact of biologic treatment on the outcomes evaluated.

The selection of patients from Reuma.pt may introduce a potential selection bias in the inclusion of the patients as it may overrepresent more severe cases and some categories of JIA, as many patients in remission could have been lost for follow-up. In this way the analysis may not be entirely representative of the whole population.

**Timeline:**

1- Starting date: 1st March 2017.

2- March-May 2017. Task 1: Selection of patients in Reuma.pt.
3- June-November 2017. Task 2,3,4,5: Patient evaluation.
4- November-December 2017: data analysis
5- January-March 2018: paper writing and submission; abstract submission to EULAR and ACR.

This study will be conducted according to the Declaration of Helsinky and will be submitted to the Ethics Committee of Hospital Santa Maria, Centro Hospitalar Lisboa Norte.

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Institutions involved: participation is open to all Portuguese centers interested in collaborating in this project that had patients included in adult JIA cohort studied in the first part of the study. Co-authorship will be granted to a maximum of 2 co-authors per center, actively collaborating in the project. Co-authorship will be dependent on the number of patients enrolled (a minimum of 5 patients per participating center is required) and on the involvement of the authors in the work to collect data and write the manuscripts.

**Funding and conflicts of interest**
This project will apply to Bolsa do Fundo de Apoio à Investigação, funded by Sociedade Portuguesa de Reumatologia.
No conflicts of interest or other external funding to declare.

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