

**Title:** Predictive factors of relapse, in patients with JIA in remission, after discontinuation of synthetic disease-modifying antirheumatic drugs.

## **Background**

Juvenile idiopathic arthritis (JIA) is not a single disease, but a term that encompasses all forms of arthritis that began before a patient is 16 years old, persist for more than 6 weeks and are of unknown origin. [1] According to disease onset, seven categories can be identified in International League of Associations for Rheumatology classification for JIA: systemic JIA, oligoarthritis, rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis, juvenile psoriatic arthritis, enthesitis-related arthritis (ERA) and undifferentiated arthritis. [2] JIA is the most common rheumatic disease of childhood, with a prevalence that varies between 16 and 150 per 100,000 children. [1,3]

Understanding the immunological mechanisms involved in the pathogenesis of the diseases allowed to develop new drugs targeting specific steps of the immune response.[4] However, classic drugs including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) remain the mainstay of pharmacological therapy of JIA due to a substantial body of evidence, long term experience and significantly smaller price tag. [5]

The Portuguese guidelines, on behalf of the Portuguese Society of Rheumatology and Portuguese Society of Pediatrics and other countries guidelines have provided a frame of reference on when and how to use DMARDs and biologic agents in the treatment of JIA. In all guidelines, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids (IAC) are considered first line therapy for oligoarticular arthritis. In case it fails, or in case of polyarticular or extended oligoarthritis presentation, methotrexate (MTX) remains the treatment of first choice. [6,7] MTX has been the most widely used first line DMARD in the treatment of JIA for more than 25 years. [5,8] When MTX is contraindicated, leflunomide is other DMARD to be considered for use in polyarticular JIA, despite the lack of approval for pediatric use. [5,9,10] For patients with ERA, sulfasalazine is the preferred choice. [5,9,11]

In a Canadian cohort study, the probability of attaining inactive disease, with contemporary treatments, exceeded 70% within 2 years in all categories, except for RF-positive polyarthritis (48%); the treatment was discontinued in 67% of patients, due to inactive disease, at least once within 5 years of follow-up. [12]

Moreover, according to a German national register database, MTX was discontinued in approximately 32% patients with JIA after achieving inactive disease. Of these, 58.2% experienced a relapse on follow-up after MTX stop (mean: 2,0 years SD=1,5). The likelihood of a disease relapse in follow-up was negatively associated with time in clinical inactive disease under MTX treatment before its discontinuation (HR 0.95; 95%CI 0.93 to 0.97). Patients with inactive disease for longer than 12 months had a significantly lower relapse rate [8].

Study rationale: There is some evidence that time spent in inactive disease before MTX discontinuation is associated with lower likelihood of relapse, while RF positive polyarthritis and extended oligoarthritis categories are associated with higher likelihood of disease relapse. Nevertheless, other predictive factors of relapse need to be studied as well as evidence for other csDMARDs besides MTX. In addition, there are no current recommendations to guide discontinuation of csDMARDs, so this study could help for the development of national recommendations.

## **Objectives**

### Primary objective:

- To identify predictive factors of relapse after discontinuation of csDMARDs in patients with JIA in remission.

### Secondary objectives:

- To calculate the proportion of patients who maintain inactive disease 12 months after withdrawal of a csDMARDs and characterize these patients.
- To calculate the proportion of patients that keeps inactive disease at 5 years and characterize these patients.
- To identify the time in inactive disease before relapse.

- To calculate the proportion of patients that restart a DMARD.
- To identify differences of relapse risk, between different forms of discontinuation of csDMARDs: when treatment is discontinued abruptly, or when tapered gradually by reducing the dosage progressively or by increasing the interval between doses.

## **Methods**

### Study design:

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

Inclusion criteria: Patients with JIA according to ILAR classification; registered in Reuma.pt; 18 years old or younger; who have reached inactive disease have and discontinued csDMARDs with available information.

Exclusion criteria: Patients never treated with csDMARDs; Patients ever treated with biologics; Patients with missing data for the main variables analysed.

### Definitions:

Disease activity will be categorized according to the 27-joint Juvenile Arthritis Disease Activity Score (JADAS27). Clinical inactive disease (CID):  $JADAS27 \leq 1$ ; Low disease activity (LDA): oligoarticular course:  $JADAS27 \leq 2,0$ ; polyarticular course:  $JADAS27 \leq 3,8$ ; [13;14] In case of missing data for JADAS 27 we will perform a JADAS 10 calculi. Inactive disease -  $JADAS10 < 1$ ; Minimal disease activity - for oligoarticular JIA  $< 2$  and for polyarticular JIA  $< 3.8$ ; Low disease activity - 5 to  $< 15$ ; Moderate disease activity - 15 to  $< 25$ ; High disease activity - 25 to  $\leq 40$ . [14;15]

Remission - inactive disease for a minimum of six consecutive months and the patient is receiving anti-rheumatic medications (clinical remission on medication) or for a minimum of 12 consecutive months after the patient has discontinued all anti-rheumatic medications (clinical remission off medication).[16]

Relapse - reoccurrence of at least moderate disease activity or restarting a DMARD.[17]

Data source:

This study will use data collection from the Reuma.pt database (no data that directly identifies patients will be collected).

Variables:

- Characteristics of disease and at study baseline (csDMARDs discontinuation) :

Demographic and clinical characteristics of patients (age, race, gender, body mass index, family history of rheumatic diseases).

Category of JIA, age at disease onset, joint involvement at the beginning of the disease, presence of extra-articular manifestations, time elapsed between onset of symptoms and diagnosis, disease activity, Physician Global Assessment and Parent/Patient Global Assessment (measured on a 10 cm Visual Analog Scale (VAS), Childhood Health Assessment Questionnaire (CHAQ), Juvenile Arthritis Damage Index (JADI), total blood count, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) value, levels of rheumatoid factor, anti-CCP antibodies and antinuclear antibodies (ANAs), presence of HLA B27 gene complex.

Forms of discontinuation of csDMARDs (abruptly, tapered gradually by reducing the dosage progressively or by increasing the interval between doses).

- Treatment:

Disease duration at the time of initiation of csDMARDs (type of drug, dosage, route of administration), treatment duration, concomitant medication (corticosteroids (dose, treatment duration and cumulative dose), NSAIDs), number of joint injections with corticosteroids and joint surgeries.

- At the time of the last visit or disease relapse (whichever occurs first):

Duration of follow-up, disease activity, time in inactive disease and low disease activity, duration of disease, relapse after discontinuation of csDMARDs, new treatments, active and/or limited, presence of extra-articular manifestations, disease activity, Physician Global Assessment and Parent/Patient Global Assessment (measured on a 10 cm VAS), CHAQ, JADI, total blood count, ESR and CRP value, relapse after discontinuation of csDMARDs, initiation of new treatments.

## **Statistical analysis**

Descriptive analysis of continuous variables will be reported as mean and standard deviation, or median and quartiles in case of non-normal distribution. Descriptive analysis of categorical variables will be displayed as frequency or proportions.

To identify differences of relapse risk, univariate analyses with the independent variables will be performed.

Time to disease relapse will be assessed by Kaplan-Meier survival analysis.

Subsequently, multivariate logistic regression models and a Cox regression will be performed to identify predictors of relapse after csDMARDs discontinuation.

Statistical analysis will be performed in the *Statistical Package for the Social Sciences (SPSS)*® v.24. The value of statistical significance for all tests was defined as 2-sided  $p < 0,050$ .

## **Expected results and possible limitations**

We expect to characterize Portuguese patients with JIA in remission who have discontinued csDMARDs and identify the predictive factors of relapse as well as the safest way to stop csDMARDs. With this we expected to improve treatment of JIA patients and contribute to adequate discontinuation of csDMARDs, in patients in remission.

Limitations such as underreporting and missing data are expected. In order to minimize missing data, all participating centers will be asked to complete the dataset with information from the medical charts, when available.

## Calendar

Timelines for the several steps of this project are presented in table 1. Globally, it is estimated that it will take 11 months to be concluded.

**Table 1. Timeline**

Task	2018								2019		
	May	June	July	August	September	October	November	December	January	February	March
Research project Elaboration and Reuma.pt approval											
Data extraction											
Data analysis											
Prepare the study final report											

## Research team

Proponents: Soraia Azevedo, Filipa Teixeira, Daniela Peixoto - Rheumatology department Unidade Local de Saúde do Alto Minho;

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

Co-authors: Authorship and co-authorship will be based in the International Committee of Medical Journal Editors and Reuma.pt guidelines.

Conflict of interest: To be completed after research team is identified

### **Ethical considerations:**

This study will be conducted according to the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies. This study will be submitted for validation and approval to the Ethics Committee of Hospital: Unidade Local de Saúde do Alto Minho and to the Coordinator and Scientific Board of Reuma.pt. Results will be presented in an objective way, and will not be hidden or manipulated.

### **References**

- [1] Ravelli A, Martini A. A Juvenile idiopathic arthritis. *Lancet*. 2007; 369:767–778
- [2] Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision. *J Rheumatol*. 2004; 31:390-392
- [3] Peterson LS, Mason T, Nelson AM et al Juvenile rheumatoid arthritis in Rochester, Minnesota 1960–1993. Is the epidemiology changing? *Arthritis Rheum*. 1996; 39:1385–1390
- [4] Vanoni F, Minoia F, Malattia C. Biologics in juvenile idiopathic arthritis: a narrative review. *Eur J Pediatr*. 2017; 176(9):1147-1153.
- [5] Hügler B, Horneff G. The Role of Synthetic Drugs in the Biologic Era: Therapeutic Strategies for Treating Juvenile Idiopathic Arthritis. *Expert Opinion on Pharmacotherapy*. 2016; 17(5):703-714
- [6] Santos MJ, Canhão H, Conde M et al on behalf of the Portuguese Society of Rheumatology and Portuguese Society of Pediatrics. Portuguese recommendations for the use of biological therapies in children and adolescents with Juvenile Idiopathic Arthritis - December 2011 update. *Act reumatol port*. 2012;37:23-43
- [7] Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013; 65(10):2499-512

- [8] Klotsche J, Minden K, Niewerth M, Horneff G. Time spent in inactive disease before MTX withdrawal is relevant with regard to the relapse risk in patients with JIA. *Ann Rheum Dis.* 2018;
- [9] Blazina, Š., Markelj, G., Avramovič, M.Z. et al. Management of Juvenile Idiopathic Arthritis: A Clinical Guide. *Pediatr Drugs.* 2016; 18:397
- [10] Alcântara AC, Leite CA, Leite AC, Sidrim JJ, Silva FS Jr, Rocha FA. A longterm prospective real-life experience with leflunomide in juvenile idiopathic arthritis. *Rheumatol.* 2014; 41(2):338-44.
- [11] Dutch Juvenile Idiopathic Arthritis Study group. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. *Ann Rheum Dis.* 2007; 66(11):1518-24.
- [12] Guzman J., Oen K., Tucker L.B., Huber A.M., Shiff N., Boire G. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. *Ann Rheum Dis.* 2014; 74(10):1854–1860.
- [13] Ravelli A, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2018; 0:1-10
- [14] Consolaro A, Bracciolini G, Ruperto N, et al. Paediatric Rheumatology International Trials Organization. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: Defining criteria based on the juvenile arthritis disease activity score. *Arthritis Rheum.* 2012 Jul;64(7):2366-74
- [15] Horneff G, Becker I. Definition of improvement in juvenile idiopathic arthritis using the juvenile arthritis disease activity score. *Rheumatology (Oxford).* 2014; 53(7):1229-34.
- [16] Wallace CA, Ruperto N, Giannini E et al. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol.* 2004;31:2290–4.
- [17] Consolaro A, Negro G, Chiara Gallo M, et al. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. *Arthritis Care Res* 2014; 66:1703–9.