ORIGINAL ARTICLES

Predictive factors of relapse after methotrexate discontinuation in juvenile idiopathic arthritis patients with inactive disease

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ABSTRACT

Objective: To identify predictive factors of relapse after discontinuation of Methotrexate (MTX) in Juvenile Idiopathic Arthritis (JIA) patients with inactive disease.

Methods: We conducted a prospective multicenter cohort study of patients diagnosed with JIA using real world data from the Portuguese national register database, Reuma.pt. Patients with JIA who have reached JADAS27 inactive disease and discontinued MTX before the age of 18 were evaluated.

Results: A total of 1470 patients with JIA were registered in Reuma.pt. Of the 119 bionaive patients who discontinued MTX due to inactive disease, 32.8% have relapsed. Median time of persistence (using the Kaplan-Meier method and log-rank tests) with inactive disease was significantly higher in patients with more than two years of remission before MTX discontinuation and in those who did not use NSAIDs at time of MTX discontinuation.

In Cox regression analyses and after adjustment for age at diagnosis, MTX tapering and JIA category, the use of NSAIDs at the time of MTX discontinuation (HR, 1.98 95%CI 1.03-3.82) and remission time of less than two years before suspension (HR, 3.12 95%CI 1.35-7.13) remained associated with relapse.

No association was found between JIA category or the regimen of MTX discontinuation and the risk of relapse.

Conclusions: In this large cohort we found that the use of NSAIDs at the time of MTX discontinuation was associated with a two times higher likelihood of relapse. In addition, longer duration of remission before MTX withdrawal reduces the chance of relapse in bionaive JIA patients.

Keywords: Clinical inactive disease; relapse; Methotrexate withdrawal; Juvenile idiopathic arthritis.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a designation that encompasses all forms of arthritis of unknown origin, that begin before the age of 16 years-old and persist for more than 6 weeks[1]. According to the 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 chronic rheumatic disease of childhood and prevalence varies between 16 and 150 per 100000 children[1, 3].

The knowledge of immunological mechanisms involved in disease pathogenesis allowed the development of 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, thanks to substantial scientific evidence, long term experience and significantly smaller price tag[5].

Different guidelines from several countries have provided a frame of reference on when and how to use csDMARDs and biologic DMARDs in the treatment of JIA. In all guidelines, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids are considered first line therapy for oligoarticular arthritis. However, methotrexate (MTX) remains the first-choice option for polyarthritis or extended oligoarthrtis presentation and a second line therapy in refractory oligoarthritis[6, 7]. MTX has been the most widely used first line DMARD in the treatment of JIA for more than 25 years[5,

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[9, 10]. Nonetheless, with an aggressive treat-to-target strategy, in polyarticular JIA, 50% of the patients achieve their therapy goal with MTX in monotherapy[8]. However, when remission is achieved, doubts remain regarding discontinuation of MTX as about half of the patients relapse after withdrawing or tapering this therapy[11].

A recent systematic literature review showed that only 4 studies addressed MTX withdrawal[12]. Of these, just two underlined the association between clinical factors and risk of flare[9, 13], and only one was prospective[9]. Moreover, studies on MTX withdrawal differ considerably in design, including remission definitions, sample sizes, withdrawal approaches, and assessed outcomes[12].

According to the German national register database, MTX was discontinued in approximately 32% patients with JIA after achieving inactive disease (316 patients). Of these, 58.2% relapsed on follow-up after MTX discontinuation (mean: 2.0 years, SD=1.5); the likelihood of disease relapse 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); also, patients with inactive disease for longer than 12 months had a significantly lower relapse rate[9].

There is some evidence that longer inactive disease state before MTX discontinuation is associated with lower likelihood of relapse, while RF-positive polyarthritis and extended oligoarthritis categories are associated with higher risk of relapse[9, 12]. Nevertheless, other predictive factors of relapse need to be studied.

Currently, the optimal tapering method has not been established and a question remains on which patients would most likely benefit from medication tapering. Therefore, the present study aimed to investigate predictive factors of relapse after discontinuation of MTX in JIA patients with inactive disease.

METHODS

Study design: This was a prospective multicenter study of patients with diagnosis of JIA using real world anonymous patient-level data from the national register database Reuma.pt[14]. We included patients with JIA according to ILAR classification[2], registered in Reuma.pt, treated with MTX monotherapy, who have reached 27-joint Juvenile Arthritis Disease Activity Score (JADAS 27) inactive disease and discontinued MTX before the age of 18 and with complete available information. Patients receiving other csDMARDs or biologics were excluded.

Study included all patients that met inclusion criteria at data extraction in September 2019.

The study was approved by the Coordinating and Scientific Committee of Reuma.pt and Ethics Committee for Health of our Hospital. Reuma.pt was approved by National Data Protection Board and by the local Ethics Committees. Written informed consent for data collection and use for research was obtained from parents/legal guardians and also form children if more than 12 years-old. Reuma.pt was established in 2008 and gathers information on effectiveness and safety of bDMARDs, csDMARDs and other treatment strategies[14]. The frequency of patient visits was recorded according to local clinical practice.

DEFINITIONS

Disease activity was categorized according to the JADAS 27. Clinical inactive disease (CID): JADAS 27 ≤ 1; Low disease activity (LDA): oligoarticular course – JADAS 27 ≤2,0; polyarticular course - JADAS 27 ≤3,815[17]. Remission was defined as inactive disease for a minimum of 6 consecutive months while 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)[18]. Relapse is characterized for the reoccurrence of at least moderate disease activity or need to restart a DMARD[19].

Time of MTX withdrawal was accounted since the last administrated dose, considered as the time of complete discontinuation.

VARIABLES

Data regarding patients and disease characteristics at MTX beginning and withdrawal, at the time of the last visit or disease relapse (whichever occurred first) and related to treatment were collected.

Baseline variables: JIA category, gender, ethnicity, body mass index (BMI), age at disease onset, age at diagnosis, family history of rheumatic diseases, years from disease onset until diagnosis and until DMARD initiation, levels of RF and anti-citrullinated peptide antibodies (ACPA); antinuclear antibodies (ANA) positivity, presence of HLA B27 gene complex, occurrence of extra-articular manifestations and comorbidities.

Follow-up variables: Follow-up duration, disease activity, joints with active disease and/or limited mobility, Physician Global Assessment (PhGA) and Parent/Patient Global Assessment (PGA) (measured on a 10 cm Visual Analog Scale (VAS)), Childhood Health Assessment Questionnaire (CHAQ), Juvenile Arthritis Damage Index (JADI), JADAS 27, total blood count, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) value, concomitant medication (corticosteroids, NSAIDs).

MTX exposure: Beginning and discontinuation date, dose, route of administration, tapper regimen.

Outcome: relapse after MTX withdrawal.

Statistical analysis: Descriptive analysis of continuous variables was reported as mean and standard deviation (SD), or median and interquartile range (IQR) in case of non-normal distribution. Descriptive analysis

of categorical variables was displayed as frequency or proportions. To identify differences in the relapse risk, univariate analyses with the independent variables were performed. Subsequently, multivariate logistic regression models and a Cox regression were performed to identify predictors of relapse after MTX withdrawal. Multivariate models were fit in enter method with time to relapse and including variables with significant association with relapse in the univariate analysis and those reported in others studies or with clinical relevance. Persistence in inactive disease was estimated using the Kaplan-Meier method and groups were compared with log-rank tests. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS)® v.24. The value of statistical significance for all tests was defined as 2-sided $p < 0.050$.

RESULTS

Study population

A total of 1470 patients with JIA were registered in Reuma.pt; 563 were 18 years-old or younger at the time of data extraction. Of these, 258 were treated with MTX and considered bio-naïve. MTX was stopped in 119 due to inactive disease (Figure 1).

Of the 119 bio naïve patients who discontinued MTX due to inactive disease, the median age at JIA diagnosis was 6.2 years-old (IQR: 7.6) and at MTX beginning 8.1 years-old (IQR: 7.9). In median, 0.79 (IQR: 1.55) years have passed from disease onset until DMARD initiation. The majority of patients (69.7%) were female and 60.6% had oligoarticular JIA. 28.6% of patients had extra-articular manifestations, with uveitis being the most frequent, corresponding to 41.2% of the extra-articular manifestations. Only 3 patients had documented comorbidities (hypothyroidism, dyslipidemia and type 1 diabetes mellitus) and the median of BMI was 18.0kg/m2 (IQR: 6.2). Sociodemographic and clinical characteristics are shown in Table I.

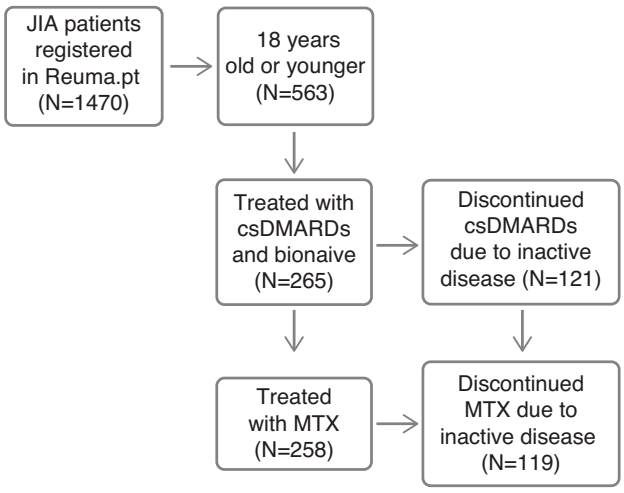

Figure 1. Patient flowchart
csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; JIA: Juvenile Idiopathic Arthritis; MTX: Methotrexate.

TREATMENT

Oral MTX formulation was the method of administration in 89.1% of the patients at time of MTX withdrawal (10.4% of these were previously treated with subcutaneous or intramuscular formulation). In addition, before MTX discontinuation, 75.6% of patients were treated with NSAIDs, 29.4% have received an intra-articular glucocorticoid injection and 21.0% were treated with oral glucocorticoids. At the time of MTX discontinuation, 38.7% of patients were under NSAIDs (even though not daily) and none were treated with oral glucocorticoids. Additionally, median MTX treatment duration was 2.8 years (IQR: 3.5) and patients were in remission for a median period of 1.3 years (IQR: 2.1). In 69.7% of the cases, MTX discontinuation was performed gradually: 90.4% progressively decreased the dose and 9.6% decreased the dose and tapered the time between intakes.

Table II shows the disease characteristics at MTX initiation and withdrawal and at relapse or last visit.

Risk of relapse after MTX discontinuation

Mean time of follow-up after MTX withdrawal was 2.9 years (SD=2.8). Relapse has occurred in 32.8% of patients on average 10.7 months [0.89 years (IQR: 1.24)] after MTX discontinuation (minimum 0.12 and maximum 3.96 years).

In univariate analysis, relapse was associated with the use of NSAIDs at the time of MTX discontinuation ($p=0.027$) and with a period of less than two years in inactive disease before MTX discontinuation ($p=0.040$).

We found no association with gender, race, RF, ACPA or ANA positivity, MTX dose, discontinuation regimen (abrupt or gradual – reducing and spacing the doses or just tapering the dose), presence of extra-articular manifestations, corticosteroid exposure, family history of anti-rheumatic disease, BMI, JADAS, JADI, CHAQ index, inflammatory parameters, tender and swollen joint counts at MTX initiation or discontinuation nor with age when inactive disease was achieved or age at MTX suspension.

The median time of persistence with inactive disease was significantly higher in patients with more than 2 years in remission before MTX discontinuation ($p=0.034$) and in those who were not under NSAIDs at time of MTX withdrawal ($p=0.026$) (Figure 2 and Supplementary tables).

In multivariable analysis, after adjustment for age at diagnosis, MTX tapering regimen and subtype of JIA,

Table I. Sociodemographic and clinical characteristics of the study population

Age at diagnosis, years (median (IQR))	6.23 (7.56)
Age at disease onset, years (median (IQR))	5.79 (7.82)
Gender %(n/N)	Female: 69.7 (83/119)
JIA categories %(n/N):	
Persistent oligoarthritis	47.1 (56/119)
Extended oligoarthritis	13.5 (16/119)
Systemic JIA	5.0 (6/119)
RF-negative polyarthritis	16.8 (20/119)
RF-positive polyarthritis	5.0 (6/119)
Psoriatic arthritis	5.9 (7/119)
Enthesitis-related arthritis	4.2 (5/119)
Undifferentiated arthritis	2.5 (3/119)
Ethnicity %(n/N):	
White of European origin	89.1 (106/119)
Other	10.9 (13/119)
Years from disease onset until DMARD initiation median (IQR))	0.79 (1.55)
Years from disease onset until diagnosis (median (IQR))	0.24 (6.8)
ANA positive (>1/160) %(n/N)	58.7 (61/104)
HLA-B27 positive %(n/N)	14.3 (9/63)
BMI (median (IQR))	18.0 kg/m2 (IQR: 6.2)
RF positive %(n/N)	7.6 (9/105)
ACPA positive %(n/N)	11.3 (6/53)
Family history of rheumatic diseases %(n/N)	10.1 (12/119)
Presence of extra-articular manifestations %(n/N)	28.6 (34/119)

ANA: antinuclear antibody; ACPA: cyclic citrullinated peptide antibody; BMI: body mass index; DMARD: Disease-modifying antirheumatic drug; HLA: human leucocyte antigen; IQR: Interquartile range; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor

only the use of NSAIDs at the time of MTX discontinuation (HR, 1.98 95%CI 1.03-3.82) and a time of inactive disease before MTX tapering less than two years (HR, 3.12 95%CI 1.35-7.13) remained associated with relapse (Table III).

Patients in remission treated with NSAID

At MTX withdrawal, 38.7% of patients were medicted with NSAIDs. No differences regarding disease characteristics at baseline were found at the time of MTX withdrawal between patients with or without treatment with NSAIDs except for joints with limited range of motion (Table IV).

DISCUSSION

In our study, two factors were identified, after adjustment for potential confounders, as relapse predictors after MTX discontinuation in JIA patients, namely the use of NSAIDs at the time of MTX withdrawal and a short time in remission before discontinuation (less than 2 years). Subclinical inflammation has been described in rheumatoid arthritis patients whose disease was considered to be in remission or with low level of activity and was demonstrated to be a predictor of relapse and radiographic progression[20]. Considering that, we hypothesized that patients medicated with NSAIDs at the time of discontinuation of MTX might not have been in "real" remission as NSAIDs could hide inflammatory manifestations. On the other hand, we found that patients that were under NSAIDs at time of MTX withdrawal had more joints with limited range of motion which can cause mechanical pain and thereby enhance NSAIDs use.

In our prospective multicenter cohort study, approximately two thirds of bionaive JIA children who stopped methotrexate due to inactive disease, remained in remission 3 years after MTX withdrawal. Our data contrasts with previous studies that report higher withdrawal rates with flares occurring in 39% of patients after 1 year of follow-up and 58% after 2.5 years[8, 11, 24].

Early diagnosis and treatment with DMARDs in JIA have vastly improved its outcomes. Currently, a large proportion of patients are able to achieve clinically inactive disease and remission, giving rise to the important question regarding DMARDs discontinuation. Given the potential adverse events and costs it may be rational to attempt to withdraw them in selected patients. However, there are no guidelines or high-quality evidence to inform clinicians on the best way and time to taper DMARDs. MTX remains the first-line csDMARD and

Table II. Disease characteristics at MTX initiation, MTX discontinuation and at last visit or disease relapse (whichever occurred first)

Disease Characteristics			
MTX treatment duration, years (median (IQR))	2.81 (3.51)		
Age at which inactive disease is reached, years (median (IQR))	10.6 (7.56)		
Age at MTX discontinuation, years (median (IQR))	12.9 (7.27)		
Relapse % (n/N)	32.8% (39/119)		
Follow-up after MTX discontinuation, months (mean±SD)	34.3 ± 33.4		
Time in remission before MTX discontinuation, years (median (IQR))	1.25 (2.06)		
Time to relapse after MTX discontinuation, years (median (IQR))	0.89 (1.24) min:0.12; max: 3.96		
Use of NSAIDs at MTX withdrawal %(n/N)	38.7% (46/119)		
History of corticosteroid exposure %(n/N)	21.0% (25/119)		
	MTX Initiation	MTX Suspension	Last visit or disease relapse
JADAS 27 (median (IQR))	10.1 (10.2)	0.00 (0.10)	1.00 (3.45)
Parent/Patient Global Assessment (median (IQR))	40.0 (37.3)	0.00 (0.00)	1.00 (13.0)
Physician Global Assessment (median (IQR))	29.0 (23.8)	0.00 (0.00)	0.00 (13.8)
Joints with limited ROM(median (IQR))	2.00 (2.00)	0.00 (0.00)	0.00 (1.00)
Tender joints (median (IQR))	3.00 (3.00)	0.00 (0.00)	0.00 (1.00)
Swollen joints (median (IQR))	2.00 (2.25)	0.00 (0.00)	0.00 (1.00)
C-HAQ (median (IQR))	0.125 (0.00)	0.00 (0.00)	0.00 (0.00)
CRP, mg/dl (median (IQR))	0.67 (1.88)	0.10 (0.18)	0.20 (0.27)
ESR, mm/hr (median (IQR))	32.5 (38.3)	8.0 (8.0)	9.0 (9.5)

NSAID: Non-Steroidal Anti-Inflammatory Drugs; C-HAQ: Childhood Health Assessment Questionnaire; cJADAS27: Clinical Juvenile Arthritis Disease Activity Score; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; IQR: Interquartile Range; MTX: Methotrexate; ROM: Range of Motion; SD: Standard Deviation

the most widely used in the treatment of JIA; however, there are very few studies addressing MTX withdrawal and risk factors of relapse. As a matter of fact, three studies published addressing that issue showed a lot of variability among pediatric rheumatologists regarding when and how to withdraw DMARDs[21-23].

In the last 30 years only 4 studies addressed MTX withdrawal[9, 11, 13, 24]. Besides these, only three evaluated MTX discontinuation with or without biologic DMARD 25-27 with a single one assessing risk of flare[25].

Hereupon, it is essential to determine the predictors of relapse after MTX suspension and how long must the patient be on CID to safely discontinue MTX. This information may minimize the risks and costs of prolonged therapy. In recent years, several authors have dedicated to this topic, however, the vast majority of studies have been retrospective and the data obtained have not been consistent, which limits the establishment of recommendations that contribute to the decision of MTX discontinuation.

In our study, flare occurred in 32.8% of bionaive JIA patients with a mean follow-up after MTX withdrawal of 2.9 years (SD=2.8), a lower rate than reported in the literature (39 to 58.2% in 12 to 30 months' follow-up)[9,11,13, 23]; this may likely reflect JIA heterogeneity and geographic differences in disease severity.

Unlike other studies that showed a higher probability of relapses in patients with RF-positive polyarthritis and extended oligoarthritis[9, 25] we found no association with JIA category. Although the subtype of JIA did not significantly affect the time to disease flare, the small sample size may have precluded detection of a significant difference.

Also, our work did not confirm the association between flare risk and age of diagnosis that was previously reported by Gottlieb BS *et al.* in a small retrospective study[13].

Like Klotsche J. *et al* study, we showed that the duration of CID state before MTX withdrawal is the greatest predictor of disease flare; patients with longer time with inactive disease before MTX discontinuation had a significantly lower flare rate[9]. This assumption was not verified in other studies[23,29] that comprised a small sample size of only 25 patients which may justify the results. Some authors propose the hypothesis that the protective effect of prolonged CID may reflect that individuals at higher risk for flare may flare sooner, even while tapering

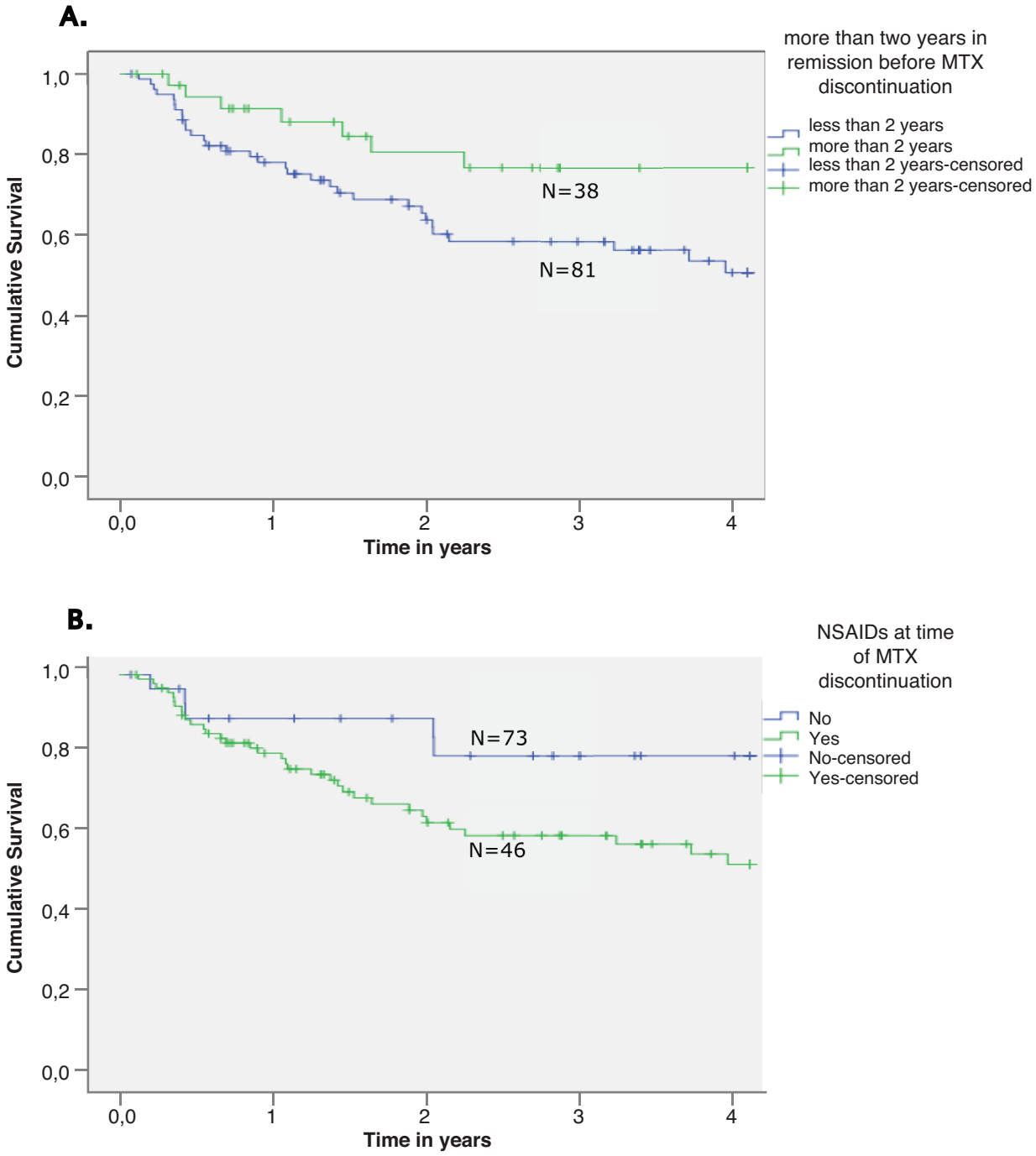

Figure 1. Kaplan-Meier survival curves showing persistence in remission by A: time in remission before MTX discontinuation and B: use of NSAIDs at the time of MTX discontinuation.
NSAIDs: nonsteroidal anti-inflammatory drugs; MTX: methotrexate.

which was classified as "depletion of susceptibles"[12].

Our study has potential limitations to consider. This is an observational study, and the decision on when and how to withdraw MTX was made by clinicians and not in a protocol-led way. We tried to minimize this bias including all national centers, taking into account all forms of discontinuation and thus making this study more "real-life" driven and thus, more similar to reality. Additionally, despite the fact that Reuma.pt database is highly used at a national level, it is not a mandatory registry and not every appointment are registered and so doses of medications like NSAIDs and corticosteroids may not be updated.

Moreover, some JIA categories, namely RF-positive

Table III. Multivariate Cox regression for relapse

Predictors*	HR	95.0% CI	p-value
Age at diagnosis	0.95	0.87-1.04	0.234
MTX tapering	0.47	0.85-4.35	0.074
NSAIDs use at the time of discontinuation	1.98	1.03-3.82	0.045
JIA category	0.90	0.37-2.21	0.591
Less than two years in remission	3.11	1.35-7.13	0.005

*In univariate analysis, relapse was associated with the use of NSAIDs at the time of MTX discontinuation (p=0.027) and with a period of less than two years in inactive disease before MTX discontinuation (p=0.040).
We found no association with gender, ethnicity, rheumatoid factor, anti-citrullinated peptide antibodies or antinuclear antibodies positivity, MTX dose, discontinuation modality (abrupt or gradual - tapering and spacing the doses or just tapering the dose),
extra-articular manifestations, corticosteroid exposure, family history, body mass index, Juvenile Arthritis Disease Activity Score (JADAS 27), Childhood Health Assessment Questionnaire index, inflammatory parameters, tender and swollen joint counts at MTX initiation or discontinuation nor with age when inactive disease was achieved or age at MTX suspension.
CI: Confidence Interval; HR: Hazard Ratio; JIA: juvenile idiopathic arthritis; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs.

Table IV. Disease characteristics at time of MTX withdrawal in patients with or without treatment with NSAID

	With NSAIDs	Without NSAIDs	p-value
MTX treatment duration, years (median (IQR))	2.65 (2.0)	3.38 (3.6)	0.881
Age at which inactive disease was reached, years (median (IQR))	8.0 (8.1)	10.4 (8.1)	0.965
Age at MTX discontinuation, years (median (IQR))	9.1 (7.6)	11.8 (7.7)	0.928
Relapse % (n/N)	45.7% (21/46)	24.7% (18/73)	0.027
JIA categories	–	–	0.074
Time in remission before MTX discontinuation, years (median (IQR))	1.57 (2.3)	1.15 (1.8)	0.432
Time to relapse after MTX discontinuation, years (median (IQR))	1.23 (1.5)	0.75 (1.2)	0.494
History of corticosteroid exposure %(n/N)	17.4% (8/46)	23.3% (17/73)	0.496
JADAS 27 (median (IQR))	0.00 (0.10)	0.00 (0.13)	0.312
Parent/Patient Global Assessment (median (IQR))	0.00 (0.00)	0.00 (0.00)	0.966
Physician Global Assessment (median (IQR))	0.00 (0.00)	0.00 (0.00)	0.315
Joints with limited ROM(median (IQR))	0.00 (1.00)	0.00 (0.00)	0.028
JADI (median (IQR))	0.00 (0.00)	0.00 (0.00)	0.999
Tender joints (median (IQR))	0.00 (0.00)	0.00 (0.00)	0.054
Swollen joints (median (IQR))	0.00 (0.00)	0.00 (0.00)	0.999
C-HAQ (median (IQR))	0.00 (0.00)	0.00 (0.00)	0.298
CRP, mg/dl (median (IQR))	0. 10 (0.1)	0.17 (0.5)	0.377
ESR, mm/hr (median (IQR))	7.0 (8.3)	11.0 (6.8)	0.488

C-HAQ: Childhood Health Assessment Questionnaire; cJADAS27: Clinical Juvenile Arthritis Disease Activity Score; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; IQR: Interquartile Range; JADI: Juvenile Arthritis Damage Index; MTX: Methotrexate; NSAID: Non-Steroidal Anti-Inflammatory Drugs; ROM: Range of Motion; SD: Standard Deviation; CI: Confidence Interval; HR: Hazard Ratio; JIA: juvenile idiopathic arthritis; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drug; – : without a global value for all the 8 juvenile idiopathic arthritis categories

polyarthritis, were underrepresented in our sample and insufficient to detect significant differences. This may reflect physician's perception of factors with worse disease prognosis and the lower likelihood of stopping MTX in RF positive patients. We cannot exclude that other variables, not retrieved by the registry and consequently not included in the analysis, may contribute to the risk of relapse.

CONCLUSIONS

In this large cohort we found that the use of NSAIDs at the time of MTX discontinuation was associated with

a two times higher likelihood of relapse. As addressed in other studies, we also showed that time in remission before MTX discontinuation is the main predictor of relapse. We found no association between the JIA category and the risk of relapse.

Key messages

- Flare occurred in 32.8% of bionaive JIA patients after MTX withdrawal.
- Use of NSAIDs at the time of MTX discontinuation and remission time of less than two years before MTX suspension were predictive factors of relapse.
- Time in remission before MTX discontinuation was the main predictor of relapse.

Ethics approval and consent to participate

The study was approved by Coordinating and Scientific Committee of Reuma.pt and Ethics Committee for Health of our hospital. Reuma.pt was approved by National Data Protection Board and by the local Ethics Committees. Written informed consent for data collection and use for research was obtained from parents/legal guardians and also form children if more than 12 years-old.

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SUPPLEMENTARY TABLES: SUBJECTS AT RISK AT EACH TIME POINT OVER THE FOLLOW-UP PERIOD

NSAIDs at the time of MTX discontinuation	Time (years)	At risk individuals
No		72
	0.94	53
	2.00	39
	3.35	26
	4.01	17
Yes	0.10	45
	1.05	29
	2.15	18
	3.16	16
	4.18	12
Time in remission before MTX discontinuation	**Time (years)**	**At risk individuals**
< 2 years	0.07	80
	1.08	54
	2.00	37
	3.16	29
	4.01	17
>2 years	0.10	37
	1.05	27
	2.25	20
	3.40	13
	4.22	12