Duration of inactive disease while off disease-modifying anti-rheumatic drugs seems to influence flare rates in juvenile idiopathic arthritis: an observational retrospective study

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ABSTRACT

Background: Many Juvenile Idiopathic Arthritis (JIA) patients reach inactivity while medicated, but there are no guidelines to determine the moment or method for discontinuing medications. We present the flare rates and remission and possible influencing factors after therapy discontinuation in children with JIA.

Methods: Data was collected from charts of JIA patients in remission on medication, who had their drugs withdrawn.

Results: Seventy patients fulfilled inclusion criteria and were included for analysis. The mean time of inactive disease on medication until tapering or withdrawal was 15.6±6.7 months; 45 (64.3%) patients remained in remission and 25 (35.7%) flared. There was no difference between groups regarding sex, age, JIA subtype, disease duration, time in remission on medication and scheme of therapy withdrawal. Patients who fulfilled Wallace criteria for remission off medication had lower flare rates than those who did not achieve 12 months of remission after the medication withdrawal ($p<0.0001$). Patients who used biologic disease-modifying anti-rheumatic drugs (DMARDs) plus synthetic DMARDs appeared to flare more (77.8% *vs* 29.5% respectively, $p=0.008$) and presented shorter periods of inactivity off medication (15.3±24.7 *vs* 32.3 ± 31.7 months respectively, $p=0.049$) compared to those who used only synthetic DMARDs.

Conclusion: It is possible that gradual drug tapering is not necessary for JIA patients, but caution must be exerted in those patients using biologic DMARDs, weighing carefully the decision to withdraw medication, due to their higher flare rates and shorter times of inactive disease after the medication withdrawal.

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INTRODUCTION

The arsenal of therapeutic options and protocols available for the treatment of Juvenile Idiopathic Arthritis (JIA) has been largely expanding over the last years; however, in the search for continuous clinical remission, many questions persist regarding the optimum moment and manner to discontinue treatment. Currently, a great proportion of patients reaches inactive disease status while medicated, but there are no guidelines as to determine for how long medications should be continued once full remission is attained, and what is the best way to discontinue therapy. The high flare rates after therapy withdrawal should be weighed against the possible side effects of continued exposure to drugs, making this a controversial topic[1,2].

Overall, disease-modifying anti-rheumatic drugs (DMARDs) are considered safe for children. However, we must consider the risk of hepatotoxicity, allergic reactions, immunosuppression, the impossibility of receiving live virus vaccines, and other potential adverse effects that may only become apparent with continuous follow-up. Furthermore, it is also important to consider the economic burden of DMARDs. Taking all these factors into account, even though the cost of therapy is evidently minimized by the gains in quality of life and reduction of articular damage, it becomes imperative to discontinue DMARDs when they are no longer necessary, thus ensuring effective use of healthcare resources and avoiding potential damage associated with unnecessary treatment[3]. It is the role of assisting physicians to aim for the ideal balance between drug withdrawal (and the risk of flare) versus continued treatment despite stable remission (and the increase in cost

and adverse effects)[4].

Considering that data regarding medication withdrawal in JIA is still scarce, the aim of this study was to present the flare rates and remission after therapy discontinuation in children with JIA treated in a Pediatric Rheumatology service, while analyzing possible influencing factors – including manner and moment of discontinuation - in disease remission.

PATIENTS AND METHODS

This was an observational retrospective study, with data collected from the charts of JIA patients of all subtypes, according to the *International League of Associations for Rheumatology* (ILAR) classification[5], who achieved clinical remission on medication and subsequently had their DMARDs fully withdrawn, either by tapering or stopping abruptly. Patients had to have used systemic drugs for the treatment of JIA (biologic and/or synthetic DMARDs), in monotherapy or in association. We did not include patients who were treated only with intraarticular corticosteroid injections or who used only hydroxychloroquine as systemic therapy. A minimum of twelve months of regular follow up after diagnosis was required.

Patients with associated comorbidities considered to have potential influence in the response to treatment or in the levels of inflammatory markers were excluded from analysis (3 patients with inflammatory bowel disease, 1 autoimmune hepatitis, 1 overlap disease, 1 TNF receptor associated periodic syndrome (TRAPS) and 1 chronic arthritis with diagnosis of juvenile systemic lupus erythematosus). We also excluded patients who, during taper, flared before they were completely off all drugs and had to return to full doses. Charts with missing or incomplete information were excluded from our sample.

We screened 278 charts of JIA patients seen in the outpatient clinic of a reference public health Pediatric Rheumatology service located in Sao Paulo – Brazil. These patients had been included in our registry from January 2015 to July 2018 (data was retrieved up to July 2019). 27 patients were immediately excluded from analysis due to missing data. 181 patients were also subsequently excluded due to any of the criteria listed above. 70 patients satisfied all requirements and were included for analysis.

The Wallace criteria[6] were used for definitions of inactive disease (no arthritis, no systemic symptoms attributable to JIA, no uveitis, normal erythrocyte sedimentation rate - ESR and C reactive protein - CRP, no disease activity on physician's global assessment), clinical remission on medication (6 months of inactive disease, while on medication), clinical remission off medication (12 months of inactive disease, while off medication).

The following schemes of withdrawal were considered: for patients using a single DMARD (monotherapy), we considered immediate withdrawal, dose tapering or increasing drug intervals until full stop; for patients in combined therapy (biologic plus synthetic DMARDs), we considered two groups: patients who had first withdrawn synthetic DMARD (immediate, tapering or increasing drug interval) and patients who initially withdrew the biologic DMARD (immediate, tapering or increasing drug interval).

Flare was defined as active disease (arthritis in one or more joints, systemic symptoms, uveitis), with or without concomitant increase in inflammatory markers, that led to a change in systemic therapy. For the purpose of this study, we did not consider disease flare in those patients who presented with single-joint arthritis and were successfully treated exclusively with intraarticular corticosteroid injections.

This study was approved by the institution's ethics committee.

Statistical analysis: qualitative measures are presented in absolute numbers and percentage and compared through Qui-square or Fisher exact test. Continuous variables are presented in mean and standard deviation, or median with minimum and maximum values; they were tested for normality and compared through the t-Student or Mann-Whitney test. For all statistical tests, we used a significance of 5%. SPSS 20.0 (IBM Corp®) was used for analysis.

RESULTS

We screened 278 JIA patients who were followed in our service from the years 2015 to 2018. Seventy patients fulfilled the inclusion criteria. Of those, 52 (74.3%) were female, most had either persistent oligoarticular (n= 26, 37.1%) or polyarticular (n=27, 38.6%) JIA subtypes. Mean age at evaluation was 15.3 ± 5.2 years.

Age at disease onset was 6.4 ± 4 years, and the time since diagnosis was 8.9 ± 3.7 years. All patients used synthetic DMARDs at some point during treatment; at

the moment of withdrawal, 59 were using methotrexate, 12 leflunomide and two cyclosporin. Only nine patients were on biologic DMARDs, all in association with synthetic drugs. Median time of disease activity from the start of therapy to inactive disease was 15 months (range 1-120 months).

The mean time of inactive disease on medication was 15.6 ± 6.7 months. 53 (75.9%) patients had their medication tapered (dose reduction or interval increase) and 17 (24.2%) patients stopped their medication immediately.

The median time after the medication withdrawal was 17.5 months (range 0-108 months) for all patients. Demographic and clinical data are listed in Table I.

Out of the 70 patients assessed, 45 (64.3%) remained in remission with a median of 24 months (range 3 – 108 months) of follow up after the medication withdrawal. Twenty-five (35.7%) patients flared at least once, with a median of 7 months (range 0 – 81 months) after the medication withdrawal. There was no difference between the patients who flared and those who did not regarding sex (p=0.41), JIA subtype (p=0.96), presence of antinuclear antibodies - ANA (p=0.66), rheumatoid factor - RF (p>0.999) or HLA-B27 (p>0.999). There was also no difference between patients who flared and those who did not regarding current age (p=0.79), age at diagnosis (p=0.6), disease duration (p=0.32), duration of active disease after treatment initiation (p=0.18), time in remission on medication (p=0.36) and scheme of medication withdrawal (p=0.26). Patients who fulfilled the Wallace criteria for clinical remission off medication (at least 12 months in remission off medication) had lower flare rates than those who could not complete a full year in remission without any DMARD (p<0.0001). Comparison of patients who flared and those who remained in remission after medication withdrawal are listed in Table II.

Only nine patients in our cohort used biologic DMARDs - six etanercept and three adalimumab – and all of them used synthetic DMARDs concomitantly, either methotrexate or leflunomide. Regarding the manner of withdrawal in this subgroup, four patients initially tapered biologic DMARD by increasing dose interval, two patients initially tapered the synthetic DMARD and three patients abruptly stopped medication, on their initiative. Seven patients (77.8%) flared, with a median of time to flare after medication withdrawal of 7 months (range 0-76 months). Of these, 6 patients (66.6%) could not achieve a full year in remission off medication

Patients who used biologic DMARDs plus synthetic

TABLE I. DEMOGRAPHIC AND CLINICAL DATA OF 70 JIA PATIENTS INCLUDED IN THIS STUDY

Characteristics	N (%)
Female sex	52 (74.3)
Age at evaluation, in years (mean ± SD)	15.3±5.2
Age at JIA onset, in years (mean ± SD)	6.4±4.0
Disease duration, in years (mean ± SD)	8.9±3.7
JIA subtype	
Persistent oligoarticular	26 (37.1)
Extended oligoarticular	3 (4.3)
Polyarticular	27 (38.6)
Enthesitis related arthritis	2 (2.9)
Systemic	9 (12.9)
Undifferentiated	3 (4.3)
Presence of antinuclear antibodies	36 (51.4)
Presence of rheumatoid factor	5 (7.1)
Presence of HLA B27[1]	2 (28.6)
Synthetic disease-modifying anti-rheumatic drug (DMARD)	70 (100)
Methotrexate	59 (84.3)
Leflunomide	12 (17.1)
Cyclosporin	2 (2.9)
Biologic DMARD	9 (12.9)
Etanercept	6 (8.6)
Adalimumab	3 (4.3)
Time of active disease following treatment initiation, in months; median (minimum-maximum)	15 (1-120)
Time of inactive disease on medication, in months (mean ± SD)	15.6±6.7
Schemes for withdrawing medication	
Immediate withdrawal of synthetic DMARD[2]	14 (20)
Dose tapering of synthetic DMARD[2]	46 (65.7)
Dose interval increase of synthetic DMARD[2]	1 (1.4)
Initial withdrawal of synthetic DMARD[3]	2 (2.9)
Initial dose interval increase of biologic DMARD3	4 (5.7)
Immediate withdrawal of both synthetic and biologic DMARDs3	3 (4.3)
Time of inactive disease after the medication withdrawal, in months; median (minimum-maximum)	17.5 (0-108)

SD – standard deviation; 1) 7 patients were tested for the antigen; 2) Synthetic DMARD in monotherapy; 3) Synthetic and biologic DMARDs in association; JIA – Juvenile Idiopathic Arthritis; HLA B27 - human leukocyte antigen B27

TABLE II. COMPARISON OF PATIENTS WHO FLARED AND THOSE WHO REMAINED IN REMISSION AFTER MEDICATION WITHDRAWAL.

	Flare (N=25)	Remission (N=45)	P-value
Female, n (%)	20 (80)	32 (71.1)	0.41
Age at evaluation, in years (mean±SD)	15.5±5	15.2±5.3	0.79
Age at JIA onset, in years (mean ± SD)	6.0±3.4	6.7±4.3	0.6
Disease duration, in years (mean ± SD)	9.4±3.9	8.5±3.6	0.32
Subtype, n (%)			0.96
Persistent oligoarticular arthritis	10 (40)	16 (35.6)	
Extended oligoarticular arthritis	1 (4)	2 (4.4)	
Polyarticular arthritis	10 (40)	17 (37.8)	
Enthesitis-related arthritis	1 (4)	1 (2.2)	
Systemic arthritis	2 (8)	7 (15.6)	
Undifferentiated arthritis	1 (4)	2 (4.4)	
Positive antinuclear antibodies, n (%)	12 (48)	24 (53.3)	0.66
Positive rheumatoid factor, n (%)	2 (8)	3 (6.7)	>0.999
Positive HLA B27, n (%)	1 (4)	1 (2.2)	>0.999
Type of drug, n (%)			0.008
Synthetic DMARD	18 (72)	43 (95.6)	
Biologic DMARD + Synthetic DMARD	7 (28)	2 (4.4)	
Duration of disease activity after treatment initiation, in months (mean±SD)	32.8±32.7	22.8±22.6	0.18
Duration of inactive disease on medication, in months (mean ±SD)	15.4±7.7	15.7±6.1	0.36
Withdrawal Scheme, n (%)			0.26
Tapering	17 (68)	36 (80)	
Immediate suspension	8 (32)	9 (20)	
Fulfillment of Wallace's criteria for remission off medication	8	37	<0.0001

SD – standard deviation; HLA B27 – human leukocyte antigen B27, DMARD – disease-modifying anti-rheumatic drug.

DMARDs flared more (77.8% vs. 29.5% respectively, p=0.008) and presented shorter periods of inactivity off medication (15.3±24.7 *vs.* 32.3 ± 31.7 months respectively, p=0.049) compared to those who used only synthetic DMARDs. There was no difference in the flare rates comparing specific synthetic DMARDs (methotrexate, leflunomide and cyclosporin).

Out of a total of 25 patients who flared, 18 (75%) restarted treatment with the medication they had used before withdrawal, 6 (25%) received new drugs and one patient was lost to follow up after the flare. Out of the 18 patients who restarted their previous treatment, 15 (83.3%) achieved inactive disease status, with a mean time of inactive disease of 7.7±5.8 months and three (16.4%) needed a change in therapy. Of the six patients who received new drugs, three (50%) achieved inactive disease status.

DISCUSSION

This was a retrospective observational study of JIA patients in clinical remission who discontinued therapy, aiming to assess possible influencing factors on disease flare rates after drug withdrawal. Out of a total of seventy patients, approximately one third had at least one episode of flare up to the moment of inclusion in this study. Patients who fulfilled the Wallace criteria for remission off medication - at least 12 months in remission off all DMARDs - had lower flare rates. We could not find an association between the method of withdrawal (taper or abrupt) and the flare rates. It seems noteworthy that the patients who used biologic DMARDs flared more (approximately three quarters flared) and had briefer periods of inactivity, compared to those who used only synthetic DMARDs – these find-

ings seem to imply that this subgroup of patients has more frequently relapsing and aggressive disease, however, due to the small sample size we cannot fully confirm this hypothesis. There was no difference in flare rates regarding subtype of JIA, presence of autoantibodies, sex, age at evaluation and age at disease onset.

Our flare rate seems to coincide with what has been reported in the literature. In studies assessing etanercept use and disease remission in JIA, Remesa *et al.* [7] reported a 59% flare rate, in a mean of 5.8 months after medication withdrawal; in Postepski's study[8], only 30.8% of patients remained in remission after biologic withdrawal; all patients in Pratisdou-Gerti's study flared[9], but with lower disease activity indices when compared to initial disease. Simonini *et al.* analysed withdrawal of different biologic agents (etanercept, adalimumab, infliximab, anakinra, rituximab and abatacept) and found a 75.6% flare rate, with a median time to flare of around six months[10]. Iglesias *et al.* reported flares in 82% of patients in a mean of 3 months after anti-TNF drugs withdrawal (in this study, synthetic DMARDs were stopped before withdrawing biologics)[11].

Both in our study and Foell's classic methotrexate discontinuation study[12], flare rates after stopping synthetic DMARDs were in the range of 25-50%, in sharp contrast with the higher flare rates of 70-80% reported in studies with biologic drugs. This seems to reinforce the idea that patients who need biologics to control disease activity do in fact flare more often, and may need a different approach regarding treatment discontinuation, compared to those who are able to achieve disease remission using only synthetic DMARDs.

An interesting finding in our study was the lower flare rates in those patients who, after medication withdrawal, remained inactive for at least twelve months, thus fulfilling the Wallace criteria for remission off medication. Although the attempt to validate the desired predictive ability of these criteria did not fully succeed[13], it did reveal that those patients who achieved a state of clinical remission, demonstrated longer periods of inactive disease than those who attained only inactive disease status. Our data brings us to the same conclusion, reinforcing the idea that the Wallace criteria is useful in evaluating the prognosis of patients who have their medication withdrawn due to disease inactivity, as it becomes less likely for patients to flare once they reach the one-year mark of inactive disease off medication.

The fact that we could not find a statistical difference in the flare rates when we compared current age, age at disease onset or sex seems compatible with what has been reported in other studies[4, 14]. We could also not find any difference regarding JIA subtype or RF positivity. In Guzman's ReAACh-Out cohort[15], children with RF+ polyarticular JIA presented worse prognosis, and were rarely able to discontinue treatment; in Baszis' study[14], no patient with RF+ polyarticular JIA remained inactive after withdrawing anti-TNF therapy. Since our inclusion criteria determined that patients had to completely withdraw all drugs to be included, it is possible that our RF+ polyarticular patients flared during tapering, justifying their small numbers in our sample, and the lack of statistical significance thereof.

We found no difference in the flare rates regarding the duration of remission on medication. This is compatible with Foell's study, in which no difference was found in flare rates in the group who stopped MTX after six months of inactivity and the group who stopped after twelve months. Simonini[10] reported that, in patients using biologics, duration of remission on medication longer than two years reduced the odds of flaring. Prince *et al*[16] also reported that using etanercept for longer periods seemed to decrease the chance of flare. Baszis *et al*[14], however, reported that treatment duration once inactivity was achieved did not have any influence on the time to flare after medication was discontinued. It is important to highlight that most of our patients were kept on medication for at least twelve months once clinically inactive, since this is the protocol in our service. This practice, although mainly empirical, is similar to what has been reported by Brought and Armon in their questionnaire of clinical practices of pediatric rheumatologists in North America[5].

It is also routine in our service to taper medication gradually, and most patients who stopped their medication abruptly did so either on their own or due to adverse effects of the medication. We could not find any difference in the flare rates in the group of patients who stopped abruptly, compared to those who tapered, suggesting that tapering as we use to do now may not be necessary, however, due to the small sample size we cannot fully confirm this hypothesis. Cai *et al*[4] suggested that progressively tapering etanercept reduced flare rates; however, in this study, no patient was taken completely off medication, making it impossible to assess chances of remission off medication. Iglesias *et al*[11] suggested that there might be a group of patients with severe disease who could benefit from continuing low doses of biologics even in sustained remission, due

to the high flares rate when medications are fully stopped.

Our study is one of the few published with pediatric patients in which all subtypes of JIA and all types of DMARDs were included. The ReACCh-Out prospective cohort also included all drugs and JIA subtypes, and reported rates of remission off medication of about 50% over 5 years, excluding the subgroup of polyarticular JIA, who had worse prognosis[15].

Limitations to our study are its retrospective nature, and the fact that it is a single-center study. We also did not use other parameters to contribute to the definition of inactive disease, such as the presence of MRP8/14 protein dosing or imaging. We highlight, however, that there is no guideline to date determining the use of new complementary methods in the assessment of JIA inactivity. Another limitation was the fact that the small sample size, especially the patients who used biological DMARDS, hampered the statistical power of our analysis.

Based on what we have observed, it could be possible that gradual drug tapering is not necessary for JIA patients, but caution must be exerted in those patients using biologic DMARDs, weighing carefully the decision to withdraw medication, due to their higher flare rates and shorter times of remission off medication. Overall, the ideal way of withdrawing medication in patients with JIA is not yet determined, and more prospective studies are necessary to create effective and safe guidelines regarding this matter. In this sense, we are expecting the results of the French clinical trial (NCT02840175 – clinicaltrials.gov), currently in active phase, which is evaluating biologic medication withdrawal (etanercept, adalimumab, abatacept and tocilizumab) in patients with inactive JIA.

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