

Analysis of arthritis flares after achievement of inactive disease with methotrexate monotherapy in juvenile idiopathic arthritis

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Abstract

Objective

To investigate the frequency of arthritis flare and factors affecting occurrence of flare in children with juvenile idiopathic arthritis (JIA) who achieved inactive disease (ID) with methotrexate (MTX) monotherapy.

Methods

A total of 217 patients were included. The modality of treatment discontinuation, time of MTX withdrawal, and disease course were examined retrospectively. For each patient, the first episode of ID after MTX start was evaluated.

Patient follow-up was censored at occurrence of flare or at last visit with persistent ID.

Results

170 patients (78.3%) had arthritis flare after a median of 1.6 years, whereas 47 (21.7%) maintained ID until last visit, after a median of 3 years. 54.2% of patients had discontinued MTX after ID, whereas 45.8% were still receiving MTX at the time of study censoring. Among patients who had MTX withdrawn, the median interval between ID and MTX stop was 1.5 years. Occurrence of flare was more common in patients who were still receiving MTX at study censoring than in those who had discontinued MTX ($p < 0.001$). Most patients (78.8%) had MTX tapered over time by increasing the interval between doses. Tapering modality was comparable between patients with flare and persistent ID. Only 7.7% of the patients had a biologic DMARD started at the time of flare.

Conclusion

Our results confirm that children with JIA who achieve ID with MTX monotherapy have a high risk of arthritis flare. The risk of flare was independent of withdrawal strategy. Most flare episodes were not treated with biologic therapy.

Key words

juvenile idiopathic arthritis, methotrexate, remission, inactive disease, treatment withdrawal

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Introduction

Methotrexate (MTX) is the most widely used synthetic disease-modifying anti-rheumatic drug (DMARD) for the treatment of juvenile idiopathic arthritis (JIA) (1-3). It has been shown to be efficacious in 60–70% of patients in randomised controlled trials (4, 5) and observational studies (6, 7). In children with oligoarthritis, concomitant administration of MTX was found to prolong and, to a lesser extent, augment the effectiveness of intra-articular glucocorticoid therapy (8). Recent studies have documented that 32.1 to 61% of patients with JIA are able to reach inactive disease (ID) with MTX monotherapy (*i.e.* with MTX as the sole DMARD) (9, 10). Once complete disease quiescence has been achieved, it would be desirable to discontinue ongoing treatment to avoid prolonged exposure of the child to the potential of side effects. It is well known that the frequency of adverse events associated with MTX therapy, particularly gastrointestinal intolerance and conditioned response (11, 12), often increases with the duration of treatment. Furthermore, the protracted administration of MTX, when given parenterally, can be challenging, particularly in younger children.

The goal of stopping treatment should be balanced with the risk of provoking disease flares after withdrawal of therapy. Flares are distressing to patients and their families, and regaining disease control may be difficult. A number of studies have documented a high frequency of disease relapses after MTX discontinuation following the achievement of disease remission in children with JIA (9, 13-15). However, currently no guidelines or recommendations are available concerning appropriate discontinuation of MTX after attainment of ID status. In particular, the optimal timing of drug withdrawal after clinical remission and the best withdrawal method are still controversial (16-18). In addition, no consistent predictors of disease flare after MTX discontinuation have been identified (16). As a result, treatment practices differ widely across clinicians and centres. A survey of North American paediatric rheumatologists has registered marked vari-

ability regarding whether and how to withdraw medications for JIA patients with clinically ID (19).

We previously found that 229 (61%) of 375 JIA patients treated with MTX monotherapy attained the state of ID after a median of 1.7 years after treatment start (10). Most of these patients were subsequently discontinued from MTX or had the medication progressively tapered. In the present study, we investigated in this patient sample the frequency of arthritis flare and the factors affecting the occurrence of flare, including the modalities of treatment withdrawal. We also compared the therapeutic interventions made at the time of disease flare with those undertaken after MTX failure in the 146 patients of the same cohort who had not achieved ID.

Methods

Study design and patient selection

The study sample was composed of the 229 patients who had achieved ID in the previous aforementioned study, which had enrolled 375 JIA patients treated with MTX monotherapy (10). The general inclusion and exclusion criteria of the study as well as the protocol of MTX administration were reported in the former paper (10). The analysis was conducted through the retrospective review of patient clinical charts and data stored in clinical databases. Patient information was collected by means of standardised case report forms and was entered in a specific excel file. For the purpose of the analysis and according to Beukelman *et al.* (20), patients were grouped in the functional phenotypes of oligoarthritis (4 or fewer affected joints), polyarthritis (5 or more affected joints), systemic arthritis, and enthesitis related arthritis (ERA). The study protocol was approved by the ethics committee of the Istituto G. Gaslini, Genova, Italy.

Assessment of ID and arthritis flare

The state of ID was defined, according to Wallace criteria (21), as no joint with active arthritis, no systemic manifestations attributable to JIA, no active uveitis, normal acute-phase reactants, and physician global assessment of overall disease activity indicating no disease

Competing interests: none declared.

Table I. Characteristics of study patients at the start of MTX therapy and during MTX administration.*

Features	All patients (n=217)	Flare (n=170)	Persistent ID (n=47)	p-value [#]
Gender				0.02
Female	189 (87.1)	153 (90)	36 (76.6)	
Male	28 (12.9)	17 (10)	11 (23.4)	
Median (IQR) age at disease onset, yrs	2.6 (1.7–5.1)	2.3 (1.6–4.6)	4.3 (2.5–7.4)	0.02
Median (IQR) disease duration at MTX start, yrs	0.9 (0.5–2.4)	0.9 (0.5–2.4)	1.1 (0.5–2.4)	0.8
Functional phenotype [§]				0.5
Polyarthritis	141 (65)	113 (66.5)	28 (59.6)	
Oligoarthritis	60 (27.6)	44 (25.9)	16 (34)	
Enthesitis-related arthritis	16 (7.4)	13 (7.6)	3 (6.4)	
Patients with positive ANA	179 (82.5)	148 (87.1)	31 (66)	0.001
Median (IQR) ESR, mm/h	36 (19–56)	40 (23.5–58)	23 (14–38.5)	<0.001
Median (IQR) CRP, mg/dl	0.89 (0.45–3)	1.1 (0.45–3.2)	0.46 (0.45–1.3)	0.7
Median (IQR) MTX dose, mg/m ² (n=X)	12.7 (11–14.3)	12.8 (11.1–14.4)	12 (10.8–14.3)	0.93
Route of MTX administration				0.46
Oral	105 (48.4)	80 (47.1)	25 (53.2)	
Parenteral	112 (51.6)	90 (52.9)	22 (46.8)	
Treatment before MTX start				
Intraarticular glucocorticoid injections	13 (6)	12 (7.1)	1 (2.1)	0.3
Systemic glucocorticoids	5 (2.3)	4 (2.3)	1 (2.1)	1
Other synthetic DMARDs	5 (2.3)	4 (2.3)	1 (2.1)	1
Concomitant therapies during MTX administration				
Intraarticular glucocorticoid injections	88 (40.5)	77 (45.3)	11 (23.4)	0.007
Systemic glucocorticoids	25 (11.5)	17 (10)	8 (17)	0.18

*Data are the number (%) unless otherwise indicated.

[#]p-value refers to the comparison between patients who did not experience or experienced disease flare.

[§]For the purposes of the study, the ILAR categories of juvenile idiopathic arthritis were grouped in functional phenotypes according to Beukelman *et al.* (20) MTX: methotrexate; ID: inactive disease; IQR: interquartile range; ANA: antinuclear antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table II. Therapeutic data of patients who flared or had persistent ID at study endpoint depending on whether they had previously stopped MTX or were still taking MTX.*

	All patients (n=216)	Flare (n=170)	Persistent ID (n=46)	p-value [#]
MTX discontinuation after ID				<0.001
Yes	117 (54.2)	81 (47.6)	36 (78.3)	
No	99 (45.8)	89 (52.4)	10 (21.7)	
Median (IQR) interval between ID and MTX stop, yrs.	1.5 (0.7–2)			
Median (IQR) interval between ID and flare or last follow-up visit with persistent ID, yrs.		1.6 (1–2.4)	3 (1.9–4.2)	0.2
Median (IQR) interval between MTX discontinuation and flare or last follow-up visit, mos.		6.7 (3–15.6)	23.7 (13.5–32.2)	0.002

*Data are the number (%) unless otherwise indicated.

MTX: methotrexate; ID: inactive disease; IQR: interquartile range.

activity (defined as score of 0 on a 0–10 visual analogue scale). In patients in whom the physician global assessment of disease activity was not available, but the other Wallace criteria were met, the absence of disease activity was inferred by consensus, as reported (10). For each patient, the first episode of ID after the start of MTX was used for the analyses. Arthritis flare was defined as the recurrence of active arthritis, defined as the presence of at least one joint with active disease (22), which prompted

the caring physician to make a major therapeutic intervention, which could include an intraarticular glucocorticoid injection, the start of systemic glucocorticoid therapy, the restart of MTX at the conventional weekly regimen, or the prescription of a biologic DMARD.

Assessment of course of MTX therapy and of disease state after achievement of ID

The clinical charts of all study patients were examined after the achievement

of ID to register the modality of discontinuation of MTX treatment (*e.g.* abrupt stop, progressive tapering), the time of MTX withdrawal, and the course of the disease over time. Patient follow-up was censored at the time of occurrence of arthritis flare or at last follow-up visit with persistent ID.

Assessment of factors affecting arthritis flare

Variables recorded at the time of MTX start comprised sex, age at disease

onset, age and disease duration, disease phenotype, antinuclear antibody (ANA) status, route of MTX administration, active joint count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The therapeutic interventions made before MTX start and the concomitant therapies during MTX administration were also registered.

Statistics

Descriptive statistics were reported as medians and interquartile ranges (IQR) for continuous variables and as absolute frequencies and percentages for categorical variables. Comparisons of quantitative variables were made using the Mann-Whitney U-test, whereas comparison of categorical data was made by chi-square test or Fisher's exact test, as appropriate. Logistic regression analysis was then performed, entering explanatory variables that showed significant results in univariate tests ($p < 0.05$) or were considered *a priori* to be of foremost importance for the study outcome, with arthritis flare as the outcome variable. Cases with missing variables were excluded from the analysis. Explanatory variables were all those listed in Table I. The step-down strategy of analysis was chosen; this consists of examining the effect of removing variables from the saturated model. The effect was expressed in terms of odds ratios, and 95% confidence intervals were calculated; statistical significance was tested by likelihood ratio test. The area under the ROC curve of the best-fitting model was used as an indicator of the predictive ability of the model. All statistical tests were two sided; a p -value of less than 0.05 was considered as statistically significant. The statistical package used was Statistica (v. 8.0, StatSoft Corp., Tulsa, OK).

Results

Patient characteristics

Of the 229 patients who achieved ID with MTX monotherapy, 12 were lost to follow-up and were, then, excluded. The remaining 217 patients were included in the study: of them, 170 (78.3%) had arthritis flare after a median of 1.6 years (IQR 1–2.4), whereas 47 (21.7%) maintained ID until last fol-

Table III. Comparison of demographic and clinical features between patients who flared after MTX discontinuation or while still taking MTX.*

Features	Flare after MTX stop (n=81)	Flare while taking MTX (n=89)	p -value [#]
Gender			0.95
Female	73 (90.1)	80 (89.9)	
Male	8 (9.9)	9 (10.1)	
Median (IQR) age at disease onset, yrs	2.4 (1.6–4.7)	2.3 (1.6–4.6)	0.96
Functional phenotype [§]			0.78
Polyarthritis	52 (64.2)	61 (68.5)	
Oligoarthritis	23 (28.4)	21 (23.6)	
Enthesitis-related arthritis	6 (7.4)	7 (7.9)	
Patients with positive ANA	72 (88.9)	79 (88.8)	0.98
Median (IQR) ESR, mm/h	45 (24.5–58)	40 (23–57)	0.64
Median (IQR) CRP, mg/dl	0.9 (0.45–3.1)	1.2 (0.45–3.3)	0.75

*Data are the number (%) unless otherwise indicated. [#] p -value refers to the comparison between patients who did not experience or experienced disease flare.

[§]For the purposes of the study, the ILAR categories of juvenile idiopathic arthritis were grouped in functional phenotypes according to Beukelman *et al.* (20).

MTX: methotrexate; IQR: interquartile range; ANA: antinuclear antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

low-up visit, after a median of 3 years (IQR 1.9–4.2). Among the 170 patients with flare, 19 (11.2%) flared within 6 months after achievement of ID, 28 (16.5%) between 6 months and 1 year, 63 (37.1%) between 1 and 2 years, 41 (24.1%) between 2 and 3 years, and 19 (11.2%) after 3 years.

Comparison between patients with flare and continued ID

The demographic, clinical and therapeutic features of the study patients, considered as a whole and by study endpoint, at the time of MTX start and during MTX administration are presented in Table I. As compared with patients who had persistent ID, patients with flare were more frequently females, had a younger onset age, were more commonly ANA positive, and had a higher ESR. The disease duration at MTX start was comparable between the two groups. The dose and route of administration of MTX as well as the other therapeutic interventions made before and during MTX administration were comparable, with the exception of a higher frequency of intraarticular glucocorticoid injections among patients who experienced arthritis flare.

The role of variables listed in Table I in predicting the occurrence of arthritis flare was, then, tested by means of a logistic regression procedure (Table VII). This analysis showed that female

patients who were ANA positive, had higher ESR and were administered more frequently intraarticular glucocorticoids during MTX therapy had a greater likelihood of experiencing arthritis flare. The lack of association between disease duration at MTX start and flare was confirmed.

Comparison between patients who had withdrawn MTX after ID or were still taking MTX at study censoring

Among the 216 patients for whom the information was available, 117 (54.2%) had been able to discontinue MTX after ID, whereas 99 (45.8%) were still receiving MTX at the time of study censoring. Among patients who had MTX withdrawn, the median interval between ID and MTX stop was 1.5 years (IQR 0.7–2) (Table II). Occurrence of arthritis flare was more common in patients who were still receiving MTX at study censoring than in those who had stopped MTX ($p < 0.001$). However, the proportion of children who were taking or no longer taking MTX was comparable among the 170 patients with flare (52.4% vs. 47.6%). The median time interval between ID and study censoring was longer in patients with persistent ID than in those with flare (3 years vs. 1.6 years). The median time interval between MTX stop and study censoring was 6.7 months in patients with

flare and 23.7 months in patients with sustained ID. The demographic and clinical characteristics of patients who flared after MTX discontinuation or while still receiving MTX were comparable (Table III).

Comparison of MTX regimens between patients with flare or sustained ID

Table IV shows the frequency of arthritis flare or persistent ID in relation to the course of MTX therapy after ID. Most patients (78.8%) had MTX tapered progressively over time, whereas 2.3% of patients had MTX discontinued abruptly, 6.5% of patients had MTX withdrawn a few months after ID without tapering, and 12.4% of patients were still receiving the standard weekly dose regimen at the time of the flare or at last follow-up visit with ID. There was no difference in the frequency of these four therapeutic regimens between patients with or without flare.

Comparison of tapering strategies

Among the 171 patients who had MTX tapered, the majority (131, 76.6%) increased the interval between doses. Alternative tapering strategies consisted in decrease in drug dosage (33, 19.3%) and switch from the subcutaneous to the oral route (7, 4.1%). The modality of tapering was comparable between patients with flare and persistent ID. The median (IQR) time interval between ID and start of MTX tapering tended to be longer in patients with persistent ID (median 7 months, IQR 2.3–15.3) than in patients with flare (median 5.3 months, IQR 0–12.3) ($p=0.07$) (Table V).

Therapeutic interventions at arthritis flare

Table VI lists the therapeutic interventions made in 168 patients who experienced arthritis flare. Most patients (122, 72.6%) were continued or resumed with MTX at standard weekly dose, 104 (61.9%) underwent an intraarticular glucocorticoid injection, 10 (5.9%) were given systemic glucocorticoids, and only 13 (7.7%) had a biologic DMARD started. In contrast, 117 of 134 patients (87.3%) of the original study (10) who had not achieved ID with MTX mono-

Table IV. Status of MTX therapy at study endpoint.*

	All patients (n=217)	Flare (n=170)	Persistent ID (n=47)	p-value [#]
Status of MTX therapy at study endpoint				0.17
MTX dosage progressively tapered	171 (78.8)	130 (76.5)	41 (87.2)	
MTX therapy still ongoing at standard weekly regimen	27 (12.4)	24 (14.1)	3 (6.4)	
MTX discontinuation after ID without tapering	14 (6.5)	13 (7.6)	1 (2.1)	
Abrupt MTX discontinuation at time of ID	5 (2.3)	3 (1.8)	2 (4.2)	

Data are the number (%).

[#]p-value refers to the comparison between patients with disease flare and those with persistent ID.

MTX: methotrexate; ID: inactive disease.

Table V. Strategies of dose reduction in patients who had MTX progressively tapered after achieving ID.*

	All patients (n=171)	Flare (n=130)	Persistent ID (n=41)	p-value [#]
Tapering strategy				0.83
Dose interval increase	131 (76.6)	99 (58.2)	32 (68.1)	
Dose reduction	33 (19.3)	25 (14.7)	8 (17)	
Switch from parenteral to oral route	7 (4.1)	6 (3.5)	1 (2.1)	
Median (IQR) interval between ID and tapering start, mos.	5.8 (0–12.4)	5.3 (0–12.3)	7 (2.3–15.3)	0.07

Data are the number (%) unless otherwise indicated.

[#]p-value refers to the comparison between patients with disease flare and those with persistent ID.

MTX: methotrexate; ID: inactive disease; IQR: interquartile range.

Table VI. Therapeutic interventions made in patients who experienced arthritis flare.*

	n (total=168)
Continuation/restart of MTX at standard weekly dose	122 (72.6)
Systemic glucocorticoids	10 (5.9)
Intraarticular glucocorticoid injection	104 (61.9)
Start of a biologic DMARD	13 (7.7)

*Data are the number (%).

MTX: methotrexate; DMARD: disease-modifying anti-rheumatic drug.

therapy were prescribed a biologic DMARD (results not shown).

Discussion

We found that a high proportion (78.3%) of our 217 patients who had reached ID with MTX monotherapy experienced a flare of arthritis a median of 1.6 years after the achievement of ID. This observation corroborates the previous reports of a high frequency of disease recurrence following attainment of ID in children with JIA (9, 13–15). The considerable flare rate seen in our cohort may depend, at least in part, on the duration of follow-up after ID, which is longer than that of most previous studies. Approximately one quarter (27.7%) of the patients flared within 1 year, where-

as the majority (61.2%) flared between 1 and 3 years. Only 11.2% had an early relapse (*i.e.* within 6 months) and an equal percentage flared after 3 years. These figures indicate that the probability of flare increased progressively over time and that many patients were able to maintain the state of ID for up to 3 years; the risk of flare among patients who had sustained ID after 3 years was low.

As compared to patients with sustained ID at last follow-up visit, patients with flare were more commonly females and ANA positive, had higher ESR, and had undergone more frequently intraarticular glucocorticoid therapy. A high female prevalence and the presence of ANA, together with an earlier age at

disease onset and a high incidence of chronic iridocyclitis, identify a subset of JIA patients that was shown to be homogeneous (23, 24) and has been placed in a separate category in a recent proposal for new classification criteria for JIA (25). Our finding suggests that children with these characteristics may be distinctly susceptible to experience flare of arthritis after MTX discontinuation. A relative increase in flare rate in patients with oligoarthritis, most of whom are known to possess the aforementioned features, was reported by Klotsche *et al.* (9). Notably, this patient subgroup have a variable course of joint disease and a marked tendency toward the spread of arthritis, with monoarticular or oligoarticular presentation and subsequent extension to polyarthritis (26). That patients with disease recurrence had undergone more frequently intraarticular glucocorticoid injection during MTX administration suggests that an increased requirement for local injection therapy may be an indication for a more prolonged administration of MTX after ID. The higher ESR value in patients who flared is in keeping with the previous demonstration of the role of this biomarker in predicting a more aggressive course of oligoarthritis (27, 28) or a higher risk of flare after intraarticular glucocorticoid injection with or without concomitant MTX (8). Around half of the patients (54.2%) had been able to discontinue MTX at the time of ID, whereas the remaining 45.8% were still receiving MTX at the time of flare or of last follow-up visit with continued ID, although most of them were in progress of tapering MTX. In patients who had MTX withdrawn, the median interval between ID and MTX stop was 1.5 years, which is longer than the minimum 12-month duration of ID required before stopping MTX by the majority of respondents to surveys among North-American and British paediatric rheumatologists (17, 19). That the occurrence of flare was more common in patients who were still receiving MTX than in those who had withdrawn the medication is paradoxical and may suggest that the former group included more patients with more severe disease than the latter.

Table VII. Best-fitted model obtained through logistic regression analysis.*

Variable	ORs	95% CI	p-value [§]
Gender: female (reference: male)	2.73	1.03 – 7.20	0.046
Disease duration at MTX start (years)	0.92	0.80 – 1.06	0.27
ANA: positive (reference: negative)	2.82	1.21 – 6.60	0.018
Erythrocyte sedimentation rate (mm/h)	1.02	1.00 – 1.04	0.027
Intraarticular glucocorticoid injections during MTX administration: yes (reference: no)	2.46	1.02 – 5.94	0.037

Area under ROC curve of the model = 0.75.

*Arthritis flare was the dependent variable. Complete data were available on 191 patients.

MTX: methotrexate; 95% CI: 95% confidence interval.

[§]By likelihood ratio test.

However, the proportion of children who were taking or no longer taking MTX was comparable among patients with flare. In addition, because the median time to flare was 1.6 years, the choice to keep MTX for at least 2 years in children with ID could have affected the observed figures. Importantly, the median time interval between both achievement of ID and MTX discontinuation and study censoring was longer in patients with sustained ID than in those with flare (3 years vs. 1.6 years and 23.7 months vs. 6.7 months, respectively), which rules out a possible bias due to shorter follow-up in patients without flare.

It is our current policy in patients who reach the state of ID with MTX monotherapy to continue the treatment at unchanged regimen for one year and then to start tapering the dose by increasing the interval between the administrations for another year until discontinuation. In line with this approach, the vast majority of the patients (78.8%) had MTX tapered progressively over time after the achievement of ID and the majority (76.6%) had the interval between the doses spaced progressively apart. Overall, the modality of treatment discontinuation did not affect the frequency of flare, although this finding should be taken with caution due to the low proportion of patients who were withdrawn from MTX through alternative methods. However, the lack of difference in flare rates between flaring strategies was found in other cohorts (29–31). The time interval between occurrence of ID and start of MTX tapering was comparable between patients with persistent ID and patients with flare. This observation differs from the find-

ing of Klotsche *et al.* (9) that a longer time spent in ID before MTX withdrawal decreased the risk of flare. The disparity between the two studies may depend, at least in part, on differences in the design, characteristics of patient population, modalities and time of MTX withdrawal, or definition of ID or flare. Furthermore, Klotsche *et al.* examined the time between ID and MTX withdrawal, whereas we evaluated the interval between ID and start of MTX tapering. Of our 44 patients with persistent oligoarthritis at MTX start, only 6 had developed polyarthritis at the time of flare. Furthermore, in contrast with the study of Klotsche *et al.*, we did not find that patients with oligoarthritis had an increased flare rate compared with the other JIA categories.

Previous clinical experiences have shown that some flares may not respond to prior treatment regimens, and require the use of more potent or expensive medications (18). In our cohort, only 7.7% of patients who experienced disease were prescribed biologic DMARDs, whereas almost two third (61.9%) underwent an intraarticular glucocorticoid injection, together with the restart or continuation of MTX at the standard weekly regimen. This finding implies that the exacerbation was not more severe than the disease state at the time of the start of MTX and was considered manageable with the same therapeutic approach. In contrast, as many as 87.3% of the 146 patients in the same study sample who had not achieved ID with MTX monotherapy were given a biologic DMARD. This disparity indicates that although children who reached ID were exposed to a high risk of flare, most disease recur-

rences were thought to be amenable to non-biologic therapeutic interventions. Our study should be interpreted in the light of some potential caveats. The design of the analysis was retrospective, which implies the risk of missing or possibly erroneous data. Our results reflect a single-centre experience, which means that they may not be generalised to series followed in other settings. Because our analysis was non-randomised and observational, the decision for MTX discontinuation was made by the caring paediatric rheumatologist based on his/her personal opinion and experience. The median time interval of 1.7 years between MTX start and achievement of ID would nowadays be regarded as too long (10). Contemporary treatment strategies mandate an earlier achievement of complete disease control (32, 33). Attainment and maintenance of this therapeutic objective is important to ensure that adolescents and young adults with JIA who are transferred to the adult rheumatology care have well-controlled disease (34). We acknowledge that due to the lack of follow-up data we could not establish whether the therapeutic interventions made at the time of the disease flare was as efficacious as the initial intervention. We should also recognise that in a number of patients the state of ID could not be established formally according Wallace criteria, owing to the lack of the physician global assessment, but was inferred through the review of clinical charts. A further limitation of our work is the lack of inclusion of uveitis in the definition of flare, which precluded the analysis of the recurrences of eye inflammation after MTX stopping. In addition, we were unable to provide information regarding whether MTX was started for joint disease, eye disease, or both. For these reasons, we did not include uveitis among the factors affecting disease flare.

In conclusion, our results confirm that children with JIA who achieve ID with MTX monotherapy have a high risk of experiencing arthritis flare after MTX withdrawal or during MTX tapering. The risk of flare was independent of the method chosen to taper MTX dosage. Most flare episodes were judged not to

be severe enough to require the introduction of a biologic DMARD. International consensus efforts and randomised controlled trials comparing different withdrawal strategies are needed to define the best strategy to prevent disease flares. Future research efforts should also aim to identify biomarkers or imaging modalities that can help making more rational the approaches to medication withdrawal in JIA.

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