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ORIGINAL ARTICLE

Risk of flare in juvenile idiopathic arthritis: Is it related to the methotrexate treatment strategy or patient characteristics?

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ABSTRACT

Objectives: The study aimed to determine the factors that increase the risk of disease flare in patients with juvenile idiopathic arthritis who stopped methotrexate (MTX) monotherapy following inactive disease (ID).

Patients and methods: In the retrospective study, files of all juvenile idiopathic arthritis cases between April 1992 and June 2022 were examined. Patients who stopped MTX monotherapy following ID were evaluated. Patients with disease flare and persistent ID were compared. Juvenile idiopathic arthritis subgroup, age of symptom onset, autoantibodies, acute phase reactants, MTX method of use, and withdrawal strategy were recorded. Systemic juvenile idiopathic arthritis patients were excluded from the study due to different clinical symptoms, diagnosis, and treatment methods.

Results: Files of 1,036 patients were evaluated, and 107 patients (88 females, 19 males; mean age: 5.9±4.2 years; range, 0.8-16.5 years) were included in the study. The median age at symptom onset was 4.8 (interquartile range [IQR]: 2-7.6) years. In terms of juvenile idiopathic arthritis subgroups, 52 (48.6%) had oligoarticular juvenile idiopathic arthritis, 43 (40.2%) had polyarticular juvenile idiopathic arthritis, and 12 (11.2%) had juvenile psoriatic arthritis. The patients reached ID in nine (IQR: 4.8-17.7) months after starting MTX, and MTX treatment was discontinued after one (IQR: 0.7-1.3) year following ID. The disease flare developed in 59 (55%) of the cases. The ID continued in 48 (45%) patients. In multivariate analysis, the risk of flare was associated with younger symptom onset (odds ratio [OR]=2.2, p=0.006), antinuclear antibody positivity (OR=1.6, p=0.03), higher erythrocyte sedimentation rate (OR=1.01, p=0.04), and C-reactive protein (OR=1, p=0.02) at the MTX onset. No difference was observed between the two groups regarding MTX dose, route of administration, prior and concomitant treatments, time to reach ID, and time and method of MTX discontinuation.

Conclusion: In this study, the risk of flare was associated with patient's characteristics, rather than the administration and discontinuation method of MTX.

Keywords: Children, flare, inactive disease, juvenile idiopathic arthritis, methotrexate.

Juvenile idiopathic arthritis (JIA) is a chronic and heterogeneous disease causing irreversible structural changes in the joints due to prolonged synovial inflammation.[1] The classification criteria of the International League Against Rheumatism divide JIA into seven subcategories.[2] All forms of JIA are associated with an increased risk of structural joint damage. The disease may continue to adulthood, resulting in significant morbidity and deterioration in the quality of life.[3] Treatment strategies aim to stop inflammation, relieve pain, maintain joint function, prevent damage, and suppress disease activity.[4,5]

Today, several treatments are available, including nonsteroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids,

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and synthetic and biological disease-modifying antirheumatic drugs (DMARDs).[6] Methotrexate (MTX) is the most commonly used agent among synthetic DMARDs in JIA treatment.[7] In randomized controlled and observational studies, treatment response has been reported in the range of 60 to 70%.[8,9]

Thanks to the developments in JIA treatment, inactive disease (ID) rates have increased under medication, it is possible to prolong the drug-free ID period by preventing disease flare in recent years.[10,11] For this purpose, studies are performed to investigate the factors that increase the risk of disease flare. Some of these studies attempt to predict the risk by examining the characteristics of the patients and the disease, and in some of them, the most appropriate treatment application and discontinuation method to prevent the disease flare is determined.[12-14] However, a precise prediction has not been provided yet, and the ideal treatment method has not been determined. Most of the studies are related to biological agents, and there are few studies on the risk of flare in patients who received MTX.[11,15,16]

Previous studies have reported that the risk of disease flare increases in girls with positive autoantibodies, multiple joint involvements at the time of diagnosis, and disease severity.[12,15-17] Various biomarkers are defined for this purpose.[13,18] However, an explicit model effective in predicting the risk of flare is not yet reported.[19] The primary objective of the study was to determine the risk factors of flare in JIA following MTX discontinuation in patients who have ID.

PATIENTS AND METHODS

Case records of all patients diagnosed as JIA according to the International League Against Rheumatism criteria[2] in the pediatric rheumatology department of the Dokuz Eylül University Faculty of Medicine, between April 1992 and June 2022 and who were followed up for at least one year were retrospectively reviewed. Systemic JIA patients were excluded from the study due to different clinical symptoms, diagnosis, and treatment methods. The absence of any synthetic or biological DMARD treatments before or during MTX treatment was defined as "MTX monotherapy." The fact that steroid, NSAID, or intra-articular injection (IAI) treatment was administered before or concomitantly with MTX was not considered an obstacle to inclusion in the study. All patients who achieved ID with MTX monotherapy and whose treatment was discontinued were included. Among these cases, patients were compared in two groups: the disease flare group and the persistent ID group. Patients with a follow-up period of less than one year after the achievement of ID were not enrolled in the study.

Inactive disease status was evaluated considering the Wallace criteria. Patients with an absence of active arthritis and uveitis, no systemic findings attributable to JIA, morning stiffness of <15 min, normal acute phase reactants, and a score of 0 in the patient global assessment were considered ID.[20]

Following ID, the MTX administration approach was changed from subcutaneous to peroral, or the dose was reduced, and in some cases, the treatment was discontinued after a while without making any changes. Data from the persistent ID group were recorded until the last follow-up visit. Data recording of patients with disease flare was terminated at the flare date.

A flare was defined as the recurrence of disease manifestations that required intensification of treatment (new treatment, additional treatment, or dose increase) after attaining ID.[12,20-22] Sex and age at symptom onset were recorded in all patient groups. Uveitis, whether at the time of diagnosis or during follow-up, was also noted.

The number of active joints at the time of diagnosis, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) values, antinuclear antibody (ANA), and rheumatoid factor results were evaluated. NSAIDs, systemic steroids, and intra-articular steroid injections applied prior to MTX were recorded. MTX dose (mg/m^2/week), route of administration (subcutaneous or peroral), concomitant NSAIDs, systemic steroids and intra-articular steroid injection treatments, and duration were also included in the data. The number of active joints, ESR, CRP, physician Visual Analog Scale, and patient Visual Analog Scale values were determined while initiating MTX and after the discontinuation due to ID. The active joint was defined as the presence of swelling in the joint

or pain/tender joint motion without swelling and limited range of motion accordingly.[21]

The method of discontinuation of MTX treatment was evaluated. ID development time, MTX discontinuation time, disease flare, and total MTX usage time were calculated. All these data were compared between the two groups of patients with flare and persistent ID. The total follow-up durations of the cases with persistent ID were determined. The type of flare (e.g., joint findings, uveitis, and fever), the number of flares, and treatments were noted.

Statistical analysis

The IBM SPSS version 26.0 (IMB Corp., Armonk, NY, USA) was used for data analysis. The compliance of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were presented using mean and standard deviation values for normally distributed variables, median, and interquartile range (IQR, 25-75%) values for nonnormally distributed variables. Categorical data were expressed as frequency and percentage. Student's t-test was used as a parametric test, and the Mann-Whitney U test was used as a nonparametric test in numerical data. The chi-square test or Fisher exact test was used to analyze categorical data. Using the possible factors determined in univariate analyses, effective independent predictors of flare risk were analyzed using logistic regression analysis. The Hosmer-Lemeshow test was used for model fit. Diagnostic decision-making features of numerical data, which were significant in this analysis in predicting the risk of flare, were analyzed by ROC (receiver operating characteristic) curve analysis. In the presence of significant threshold values, sensitivity and specificity of these limit values were calculated. A p-value <0.05 was considered statistically significant.

RESULTS

Among the files of 1,036 patients with JIA, a total of 333 patients were identified as MTX monotherapy, and ID was achieved in 112 (33%). However, five of these patients were not included in the study since the follow-up periods after ID were less than one year. The total number of patients included in the study was 107 (107/333, 32%; 88 females, 19 males; mean age: 5.9±4.2 years; range, 0.8-16.5 years). The median age at symptom onset was 4.8 (IQR: 2-7.6) years. In terms of JIA subgroups, 52 (48.6%) had oligoarticular JIA, 43 (40.2%) had polyarticular JIA, and 12 (11.2%) had juvenile psoriatic arthritis. It was determined that the patients reached ID in nine (IQR: 4.8-17.7) months after starting MTX, and MTX treatment was discontinued after one (IQR: 0.7-1.3) year following ID. The median duration of the ID before the cessation of MTX treatment was one (IQR: 0.7-1.3) year (Table 1). The disease flare developed in 59 (55%) of the cases. ID persisted in 48 (45%) patients (Table 1).

Comparison of cases with flare and persistent ID after discontinuation of MTX

Children with younger age at symptom onset had significantly more flares (p=0.005). The ANA positivity was more frequent in cases with flare (79.7% *vs.* 45.8%, p=0.02, Table 1). The disease flare group has significantly higher CRP (7.7 mg/L) and ESR (35 mm/H) values, whereas these parameters were 2.4 mg/L and 20 mm/H, respectively, in patients with persistent ID (p=0.002 and p=0.004, respectively; Table 1). No difference was observed between the two groups regarding other demographic data, laboratory findings, MTX dose, route of administration, prior and concomitant treatments, time to reach ID, and time and method of MTX discontinuation (Table 1).

Follow-up of flare and persistent ID cases

The flare occurred 8.6 months (IQR 4.4-13) after MTX discontinuation. Patients with disease flare predominantly had joint findings (95.5%), followed by uveitis (10.4%). These cases most frequently used MTX (80.6%), NSAIDs (62.7%), and IAI (29.9%), respectively. In the disease flare group, 70.1% of the patients experienced flare once, 20.9% experienced it twice, and 9% thrice during the follow-up. The mean follow-up duration from the diagnosis to the first flare was calculated as 3.8±2.6 years, whereas the mean follow-up time of the cases with persistent ID was 4.1±2.7 years (Table 1).

Table 1. Comparison of the flare and persistent ID groups

	Persistent ID (n=48)					Flare (n=59)					All patients (n=107)					
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Median age at symptom onset (year)				6.6	3-9.8				3.2	1.6-6.5				4.8	2-7.6	**0.005**
Sex																
Female	41	85.4				47	79.7				88	82				0.43
JIA subgroup																0.56
Oligoarticular JIA	21/52	40.4				31/52	59.6				52/107	48.6				
Polyarticular JIA	22/43	51.2				21/43	48.8				43/107	40.2				
Juvenile psoriatic arthritis	5/12	41.7				7/12	58.3				12/107	11.2				
Time from disease onset to diagnosis (month)				3.5	1.8-11.7				3	1.5-4				3	1.5-6.1	0.8
ANA positivity	22/48	45.8				40/59	79.7				62/107	58				**0.02**
RF positivity	0/48	0				1/59	1.6				1/107	0.9				1
Uveitis	5/13	10.4				8/13	13.6				13/107	12				0.6
Treatments prior to MTX	36/48	75				42/59	71				78/107	73				0.6
NSAIDs	35/36	97				40/42	95				75/78	96				1
IAI	6/36	16				13/42	31				19/78	24				0.2
Systemic steroid	3/36	8				4/42	9.5				7/78	9				1
MTX initiation																
ESR (mm/h)				20	9-34				35	17-54				28	14-43	**0.004**
CRP (mg/L)				2.4	0.8-6.5				7.7	4.3-14.6				5.7	1.5-12	**0.002**
Active joints count				4.5	1-12				4	2-10				4	2-10	0.3
Physician VAS				5	3-7				6	4-7				6	3-7	0.6
Patient VAS				6.5	3-8				6	4-8				6	4-8	0.9
Dose of MTX (mg/m^2/week)			13.4±3.02					14.7±3.5					14±3.3			0.9
Administration route of MTX																0.23
Peroral	15/48	31				25/59	42				40/107	37.4				
Subcutaneous	33/48	69				34/59	58				67/107	62.6				
Concomitant treatments with MTX	31/48	65				35/59	59				66/107	66				0.57
NSAIDs	22/31	71				25/35	71.4				47/66	71.2				0.9
IAI	8/31	26				5/35	14				13/66	19.6				0.2
Steroid	11/31	35.5				14/35	40				25/66	37.8				0.7
Dose of steroid (mg/kg/day)				1	0.6-1				1	0.5-1				1	0.5-1	0.8
Duration of steroid (month)				4	3-7				3.5	2-8				4	3-8	0.7
Time from MTX onset to ID (month)				10	3.5-19.9				8.4	4.9-15.7				9	4.8-17.7	0.6
Time from ID to MTX discontinuation (year)				1	0.8-1.28				1	0.6-1.4				1	0.7-1.3	0.29
Discontinuation method of MTX																0.9
After ID without any changes	36/48	75				44/59	74.6				80/107	75				
Dose reduction and/or change administration route after ID	12/48	25				15/59	25.4				27/107	25				
During MTX discontinuation																
ESR (mm/h)				9.5	5-13				10	7-36				10	6-15	0.15
CRP (mg/L)				0.8	1.5-3				1.1	0.4-2.1				1	0.4-1.7	0.19
Active joint count				0	0				0	0				0	0	-
Physician VAS				1	0-2				1	0-3				1	0-3	0.11
Patient VAS				1	0-3				2	1-3				1.5	0-3	0.2
Total MTX usage time (year)				2	1.3-3.1				1.9	1.2-2.6				1.9	1.3-2.8	0.24
Follow-up time (year)			4.1±2.7					3.8±2.6*					-			-

ID: Inactive disease; SD: Standard deviation; IQR: Interquartile range; JIA: Juvenile idiopathic arthritis; ANA: Antinuclear antibodies; RF: Rheumatoid factor; MTX: Methotrexate; NSAIDs: Non-steroidal anti-inflammatory drugs; IAI: Intra articular injections; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: Visual analog scale; * Follow-up time between diagnosis to flare.

Table 2. Best-fitted model obtained through multivariate logistic regression analysis and cut-off values from ROC curve

	OR	95% CI	*p*	Cut-off values	Sensitivity (%)	Specificity (%)
ANA positivity	1.6	0.5-2.3	0.03	-	-	-
CRP elevation at MTX onset (mg/L)	1	0.89-1.01	0.02	6.4 AUC 0.67 p=0.002	67.8	68.7
ESR elevation at MTX onset (mm/H)	1.01	1-1.03	0.04	30.5 AUC 0.66 p=0.004	61	60.4
Younger age at symptom onset (years)	2.2	1.03-4.8	0.006	5.9 AUC 0.66 p=0.003	66.1	60.4

ROC: Receiver operating characteristic; OR: Odds ratio; CI: Confidence interval; ANA: Antinuclear antibodies; CRP: C-reactive protein; MTX: Methotrexate; ESR: Erythrocyte sedimentation rate; AUC: Area under curve.

Results of logistic regression and ROC analyses

In multivariate analysis, ANA positivity (odds ratio [OR]=1.6, p=0.03), CRP and ESR elevation at MTX onset (OR=1, p=0.02; OR=1.01, p=0.04, respectively), younger age at symptom onset (OR=2.2, p=0.006) were determined as factors increasing the risk of flare. The backward stepwise method was applied in logistic regression analysis. The p-value calculated with the Hosmer-Lemeshow test applied for model compliance was 0.59. ROC analysis was performed on this model's numerical data, and cut-off values were determined. Accordingly, the risk of flare increased in cases with a CRP >6.4 mg/L (area under the curve [AUC]=0.67, p=0.002) and ESR >30.5 mm/H (AUC=0.66, p=0.004) at the onset of MTX and an age <5.9 years (AUC=0.66, p=0.003) at symptom onset (Table 2). Youden index calculations for the cut-off values determined for numerical data resulted in <0.5.

DISCUSSION

Methotrexate is a drug that has been used in the treatment of JIA for many years and is an effective monotherapy.[13] Studies have demonstrated that 30.9 to 56.4% of patients achieved ID 6 to 11.5 months after starting MTX.[23-26] Similar to the literature, in 107 (32%) of 333 patients who received MTX monotherapy, ID was achieved nine (IQR: 4.8-17.7) months after the start of MTX in this study.

There are a few studies investigating the risk of flare in JIA patients with MTX therapy.[11,15,16,27] Only one of the studies investigated the effect of the time to reach ID on flare risk and found no difference.[27] Similarly, the time to reach ID had no effect on flare risk in our study. This is probably due to the similarity of disease activity-related factors between the two groups at the onset of MTX therapy. On the contrary, Teh et al.[27] reported this period as >6 months, increasing the risk of flare 2.2 times.

In this study, the median time to discontinue MTX treatment was one (IQR 0.7-1.3) year after ID, and disease flare was observed in 55% of the patients with a median of 8.6 months (IQR 4.4-13) following discontinuation of MTX. Other studies have similar results.[11,15,16] However, there is no consensus in the literature about the duration of MTX treatment following ID. This study found no relevance of duration on the risk of flare. Bava et al.[15] also found no difference in 216 JIA patients following MTX discontinuation after 1.5 years of ID. Foell et al.[11] reported that the discontinuation of MTX treatment at 6 or 12 months after ID did not affect the risk of disease flare, similar to this study. In only one study, researchers reported that the risk of a flare was lower in patients with a persistent ID of 12 months on MTX.[16] Current data is still limited and controversial.

Regarding the risk of disease flare, Gottlieb et al.[27] reported the cut-off value for the age of onset as <4.5 years. It was found as <6 years by Guzman et al.[12] Halyabar et al.[28] reported that the

younger age of disease onset increases the risk of flare in a systematic literature review.[27-29] Similarly, this study had a cut-off value of <5.9 years. Bava et al.[15] reported that the age of disease onset in cases with the flare was lower than in cases with persistent ID; however, they did not mention a specific cut-off value. The high risk of disease flare must be taken into consideration, particularly in children with JIA younger than six years old.

Antinuclear antibody positivity increased the risk of flare 1.6 times in this study, which was approximately similar with the result of Klotsche et al.[16] (OR=1.4). Guzman et al.[30] developed a model that can calculate the probability of early remission in patients with JIA. ANA positivity was identified in this online calculator as having a negative effect on the probability of remission. Supporting our results, it was revealed that ANA-positive patients and patients with a younger age of onset developed more joint involvement over time and had a higher risk of uveitis, concluding that this group of patients should be evaluated in a separate category.[31,32] In recent years, the Pediatric Rheumatology European Society has been working on a new set of criteria, which classifies ANA-positive JIA as a separate category.[33]

In this study, NSAIDs, systemic steroid treatments, and IAIs used before and in combination with MTX did not make a difference in disease flare. Klotsche et al.[16] reported that additional treatments applied, similar to our study, did not make a difference in terms of flare. Bava et al.[15] found that the administration of IAI concomitant with MTX was higher in the group with flare. The researchers concluded that the duration of MTX use after ID should be longer in patients requiring IAI with MTX. Although the treatments applied before and concomitant with MTX are effective in disease control, no effect on the risk of flare has been demonstrated.

High CRP (>6.4 mg/L) and high ESR levels (>30 mm/H) at MTX onset increased the risk of flare in our patients. Foell et al.[11] reported that ESR and CRP values at the time of diagnosis did not affect the flare rate. They proposed new parameters such as myeloid-related proteins 8 and 14 to determine the risk group. High levels of myeloid-related proteins during remission were correlated with a high risk of flare.[11] However, current studies reflecting real-world data have shown that high ESR and CRP levels increase the risk of flare.[15,34] High CRP and ESR levels at the beginning of treatment are thought to be important factor that increases the risk of flare.

The effects of different administration approaches and the efficacy of different doses of MTX were investigated. Klein et al.[35] revealed that peroral and subcutaneous administration were equally effective. Ruperto et al.,[8] on the other hand, reported that subcutaneous MTX treatment was effective at a dose of 15 mg/m^2/week, and it did not provide any additional benefit above this dose. There was no effect of administration route and dose of MTX on risk of flare in our study. Studies on the risk of flare, consistent with our study, have reported that dose and route are not effective factors.[15,16,27,36]

Treatment was discontinued in 76.8% of the patients without changing the MTX dose and route of administration in this study. There was no effect of MTX discontinuation methods on the risk of flare. Bava et al.[15] and Klotsche et al.[16] similarly found no effect of either the dose or route of administration.

There are studies on the definition of disease flare, but complete standardization has not been achieved in this regard.[21,22] Halyabar et al.[29] wrote a systematic review and found heterogeneity between studies about uveitis in the definition of flare: Only nine of 23 studies included an absence of uveitis as disease remission. Bava et al.[15] also did not consider uveitis as a flare and reported this as a limitation of the study. In this study, uveitis is regarded as an important factor in terms of ID, as it is in the criteria of Wallace et al.[20] There was no effect of uveitis prior to ID on the risk of flare.

There are some limitations to this study. This is a retrospective, single-center study. Nevertheless, it is valuable as it reflects 30 years of real-world data of our center. In addition, it was managed by two physicians who used similar and standard treatment and follow-up algorithms. Our inclusion and exclusion criteria were clearly identified, and thus, a homogeneous study group free from confounding factors was obtained. The exclusion of patients with systemic JIA who were different from other JIA subgroups in terms of diagnosis, treatment, and clinical findings increased the strength of the results obtained. Furthermore, all factors likely to increase the risk of flare were examined. The definition of ID was met with

Wallace's criteria.[20] The follow-up period of the patients was relatively long compared to similar studies. However, the sensitivity and specificity of the cut-off values determined by ROC analysis for the age of symptom onset and CRP level at the onset of MTX were not high enough, and Youden indexes of these values were calculated as <0.5. Although the clinical predictive power of the determined cut-off values is low, the effect of variables on increasing the risk of disease flare is significant.

In conclusion, our results confirmed that variables such as MTX dose, route of administration, prior and concomitant medications, and time of MTX discontinuation did not affect the disease flare in patients with JIA. This risk is mainly affected by patient- and disease-related factors, such as ANA, CRP, and ESR levels and age of symptom onset. Prospective studies on biomarkers that may predict the risk of disease flare in JIA are required.

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Non-interventional Clinical Research Ethics Committee (date: 05.01.2022, no: 2022/01-40). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceived of the presented idea: E.Ü., B.M.; Developed the theory and performed the computations and analysis: R.İ.; Verified the analytical methods: R.T., T.A., Z.K.; Supervised the findings of this work: E.Ü., B.M.; All authors discussed the results and contributed to the final manuscript.

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