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Research Letter

Relapse and Remission in Children With Chronic Noninfectious Uveitis Treated With Methotrexate

To the Editor:

Pediatric chronic noninfectious uveitis (NIU) can lead to sight-threatening complications and often requires long-term immunosuppression. Uveitis occurs in isolation (ie, idiopathic NIU), or is associated with systemic diseases, most commonly juvenile idiopathic arthritis (JIA). Anterior involvement is most common. Tapering and discontinuation of medication are considered in children after 2 years of disease remission without taking topical glucocorticoids (GCs). However, relapse occurs in 43% to 74% within 18 months.[1-6] Our aim is to describe outcomes following discontinuation of methotrexate (MTX) in a pediatric NIU cohort.

This retrospective study was conducted in children with NIU who were enrolled in a uveitis epidemiology study, the Longitudinal Outcomes in Childhood Uveitis Study (LOCUS), at Emory Children's Center from September 2011 to July 2017. This study complied with the Declaration of Helsinki and received approval from the Emory University Institutional Review Board (IRB00017214). Informed consent/assent was obtained.

Inclusion criteria were as follows: (1) a diagnosis of chronic NIU requiring treatment with MTX for NIU; (2) use of MTX monotherapy; and (3) attempted tapering or discontinuation of MTX. Tapering is defined as decreasing the dose or frequency of the medication according to the provider's preference. Discontinuation is defined as stopping medication.

Relapse of uveitis was defined as such: (1) previously inactive NIU that is now active according to the Standardization of Uveitis Nomenclature criteria[7]; (2) addition of topical GCs or systemic therapy; and/or (3) development of new or worsening ocular complications. Remission was defined as inactive NIU for at least 3 months and not needing topical or systemic therapy. The primary outcome was time to relapse after the tapering or discontinuation of treatment. Time to relapse was described using estimates of survival derived from Kaplan-Meier (KM) survival curves with associated 95% CIs.

Of 82 children treated with MTX for NIU, 32 (39%) received MTX as monotherapy, and 13 children with inactive NIU either tapered or discontinued MTX. Of these 13, MTX was started after a median duration of uveitis of 0.8 (IQR 0.3-1.9) years, wherein 9 were on MTX by subcutaneous route and 4 were on oral route. Eleven (85%) children tapered over a median of 8 months, while 2 (15%) discontinued MTX without tapering. Demographic and clinical disease features are found in the Table and Supplementary Table (available with the online version of this article).

Eight of the 13 children discontinued MTX. Of these 8, 6 tapered and 2 discontinued without tapering. The median

Table. Characteristics of children with uveitis treated with methotrexate (MTX).

	N = 13
Demographics	
Sex, female	11 (85)
Race	
White	3 (23)
Black	5 (38)
Other	5 (38)
Etiology of uveitis	
JIA-associated	7 (54)
Non-JIA–associated	6 (46)
Elevated ACE	2 (15)
Idiopathic	3 (23)
Unknown	1 (8)
Age at uveitis diagnosis, yrs	9.9 (4.6-12.7)
Duration of uveitis at last follow-up[a], yrs	5.7 (4.4-6.2)
Uveitis characteristics	
Location	
Anterior	9 (69)
Intermediate	2 (15)
Panuveitis	2 (15)
Bilateral disease	9 (69)
History of ocular complications	
Cataracts	9 (69)
Synechiae	8 (62)
Cystoid macular edema	5 (38)
Band keratopathy	4 (31)
Glaucoma	3 (23)
MTX administration	
Tapered/discontinued MTX	
Subcutaneous MTX	9 (69)
Oral MTX	4 (31)
Age at start of MTX, yrs	11.4 (5.2-13.2)
Duration of uveitis before starting MTX, yrs	0.8 (0.3-1.9)
MTX tapering/discontinuation	
Age at start of MTX, yrs	12.8 (6.9-15.7)
Reason for discontinuation[b]	
Remission/inactive disease	13 (100)
Patient/parent preference	1 (8)
Insurance	3 (23)
Allergic reaction	0 (0)
Infections	0 (0)
Discontinued without tapering	2 (15)
Duration on MTX at time of tapering/discontinuation[c], yrs	1.4 (1.1-2.3)
Sustained remission	4 (31)
Duration of remission, yrs	1.2 (0.6-3.2)
Relapsed/restarted MTX	9 (69)
Time to MTX relapse/restart , yrs	1.2 (0.6-1.5)

Values are expressed as n (%) or median (IQR). [a] Duration of uveitis was calculated as time between dates from uveitis diagnosis to last study visit or at the start of treatment, as appropriate. [b] > 1 reason for discontinuation may apply. [c] Duration of treatment was calculated as time from start of medication to discontinuation or last study visit. ACE: angiotensin-converting enzyme; JIA: juvenile idiopathic arthritis.

duration on MTX at the time of discontinuation was 1.4 (IQR 1.1-2.3) years. Nine of the 13 children (69%) relapsed and restarted medication at a median of 1.2 years (IQR 0.60-1.5; Table and Supplementary Table, available with the online version of this article). The 4 children who sustained remission after discontinuing MTX had a similar median duration of MTX therapy (1.4 vs. 1.6 yrs) compared to the 9 who did not sustain remission.

At the time of MTX tapering/discontinuation, KM estimates suggest that 7.7% (95% CI 1.1-43.4) relapse within 3 months, 15.4% (4.1-48.8) within 6 months, 31.6% (13.2-64.1) within 1 year, and 48.7% (25.4-78.1) within 18 months (Figure).

We sought to examine the ability to successfully discontinue MTX in patients with pediatric NIU. Our results confirm that most children relapse within 2 years of tapering or discontinuation. Higher risks of relapse have been reported in patients with shorter duration of treatment, younger age at withdrawal, late start of treatment, late control of NIU activity, and JIA-associated uveitis.[2-6,8] JIA was the most common systemic disease associated with NIU in our cohort, comprising > 50% of cases. It has been shown that remission is less likely in uveitis associated with JIA.[2]

Few studies have investigated systemic treatment discontinuation in children. Reports of relapse of NIU occur in 43% to 69%.[1,3,4,6,8] Factors associated with remission in various studies include treatment with systemic medication for > 3 years, treatment within the first 6 months of NIU, and inactive NIU for longer than 2 years before discontinuation. Additionally, patients treated at a younger age and earlier in their disease course had a lower rate of NIU recurrence.[4] Guidelines from the American College of Rheumatology/Arthritis Foundation and the Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative recommend at least 2 years of remission without taking topical GCs prior to attempting taper.[9,10] In our cohort, patients were started on MTX at a median of 0.8 years and maintained for a median of 1.4 years at time of tapering or discontinuation, which supports that treatment within the first 6 months is important and that attempts at discontinuing medication may have occurred too early.[2] This may have contributed to the observed high rates of relapse.

Limitations of our retrospective study include the small sample size, inclusion of children diagnosed with different types of NIU, missing data on whether tapering occurred by dose or frequency, and limited duration of follow-up.

In conclusion, children with NIU are at increased risk of relapse after tapering or discontinuation of systemic immunosuppression. In our cohort, most children were unable to discontinue MTX, and relapse occurred within 12 months. Further study on factors associated with successful drug-free remission are needed.

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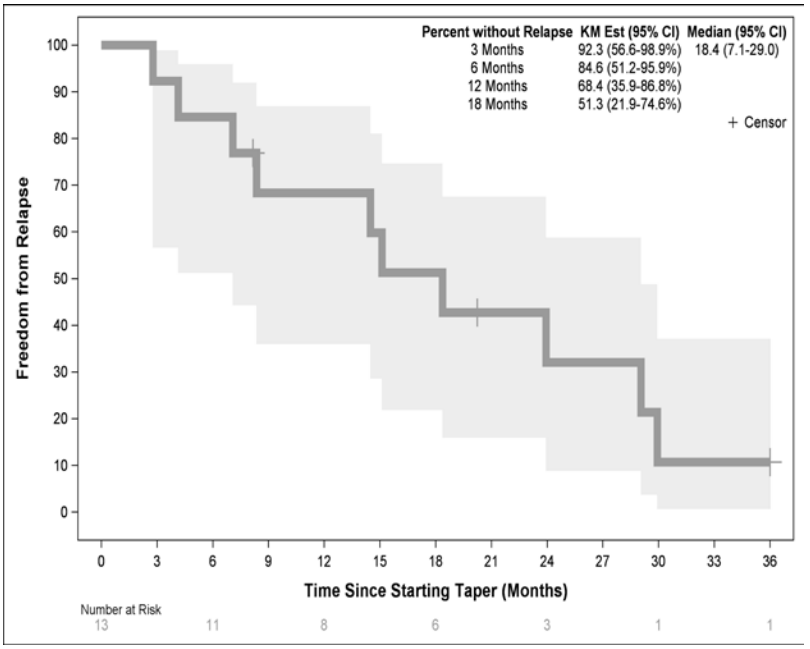

Figure. Kaplan-Meier (KM) estimates for time to relapse on methotrexate.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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