The Journal of Rheumatology 2022;xx:xxxx
doi:10.3899/jrheum.220007
First Release August 15 2022

The Journal of Rheumatology

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.

© 2022 The Journal of Rheumatology

Downloaded on April 18, 2024 from www.jrheum.org

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.

Courtney McCracken[1], PhD
Jessica G. Shantha[2], MD
Steven Yeh[3], MD
Kirsten Jenkins[4], BS
Kelly A. Rouster-Stevens[4], MD, MS
Scott R. Lambert[5], MD
Sampath Prahalad[1,4,6], MD, MS
Carolyn Drews-Botsch[7], PhD
Sheila T. Angeles-Han[8], MD, MSc
[1]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia;
[2]Francis I. Proctor Foundation for Research in Ophthalmology, and Department of Ophthalmology University of California, San Francisco, San Francisco, California;

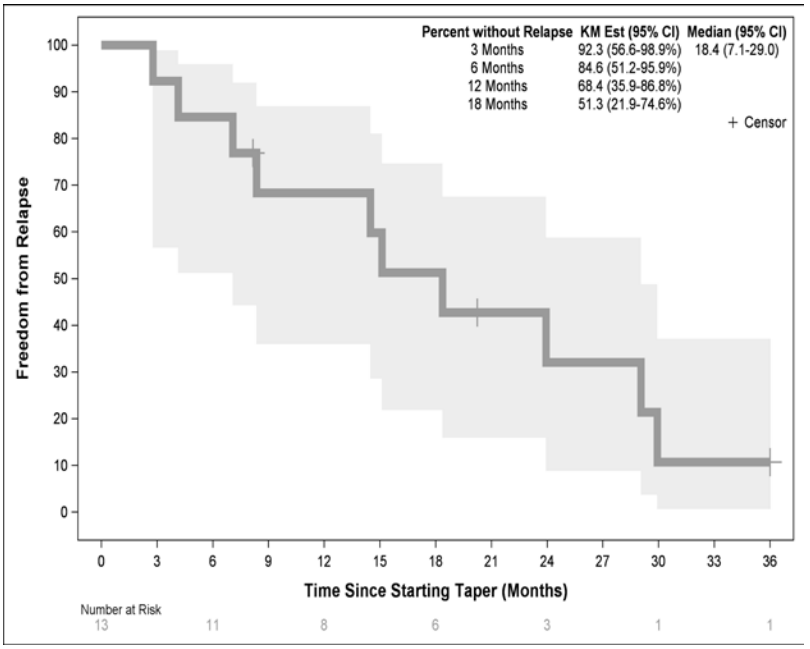

Figure. Kaplan-Meier (KM) estimates for time to relapse on methotrexate.

Downloaded on April 18, 2024 from www.jrheum.org

[3]Department of Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska;
[4]Children's Healthcare of Atlanta, Atlanta, Georgia;
[5]Department of Ophthalmology, Stanford University, Stanford, California;
[6]Department of Genetics, Emory University School of Medicine, Atlanta, Georgia;
[7]Department of Global and Community Health, George Mason University, Fairfax, Virginia;
[8]Division of Rheumatology and Pediatric Ophthalmology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, USA.

C. McCracken and J.G. Shantha contributed equally to this work.

Research reported in this manuscript was supported by the National Eye Institute (NEI) Award Number K23EY021760 (STAH), K23EY030159 (JGS), and the Rheumatology Research Foundation. STAH is also supported by NEI R01EY030521. SP is supported in part by a grant from the Marcus Foundation Inc., Atlanta.

SY is a consultant for Santen and Clearside Biomedical, unrelated to this study. KARS is a consultant for Accordant, unrelated to this study. SP serves on the Macrophage Activation Syndrome Adjudication Committee for Novartis and is a Doximity Op-Med Fellow for 2021–22, unrelated to this study. The remaining authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. S.T. Angeles-Han, Division of Rheumatology, Cincinnati Children's Hospital Medical Center, 3333 Burnett Avenue, Cincinnati, OH 45229, USA; Department of Pediatrics, University of Cincinnati, Cincinnati, OH 45229, USA.
Email: sheila.angeles-han@cchmc.org.

ACKNOWLEDGMENT

The authors would like to acknowledge Daneka Stryker, Anna Tramposch, Bessie Frias, and Steven Tommasello for medical chart review and data entry.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Lerman MA, Lewen MD, Kempen JH, Mills MD. Uveitis reactivation in children treated with tumor necrosis factor alpha inhibitors. Am J Ophthalmol 2015;160:193-200.
2. Simonini G, Bracaglia C, Cattalini M, et al. Predictors of relapse after discontinuing systemic treatment in childhood autoimmune chronic uveitis. J Rheumatol 2017;44:822-6.
3. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. Am J Ophthalmol 2011;151:217-22.
4. Saboo US, Metzinger JL, Radwan A, et al. Risk factors associated with the relapse of uveitis in patients with juvenile idiopathic arthritis: a preliminary report. J AAPOS 2013;17:460-4.
5. Acharya NR, Ebert CD, Kelly NK, et al. Discontinuing adalimumab in patients with controlled juvenile idiopathic arthritis-associated uveitis (ADJUST-Adalimumab in Juvenile Idiopathic Arthritis-associated Uveitis Stopping Trial): study protocol for a randomised controlled trial. Trials 2020;21:887.
6. Shakoor A, Esterberg E, Acharya NR. Recurrence of uveitis after discontinuation of infliximab. Ocul Immunol Inflamm 2014; 22:96-101.
7. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature Working G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-16.
8. Acharya NR, Patel S, Homayounfar G, et al. Relapse of juvenile idiopathic arthritis-associated uveitis after discontinuation of immunomodulatory therapy. Ocul Immunol Inflamm 2019; 27:686-92.
9. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. Arthritis Rheumatol 2019;71:864-77.
10. Constantin T, Foeldvari I, Anton J, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis 2018;77:1107-17.

Downloaded on April 18, 2024 from www.jrheum.org