The methotrexate polyglutamate assay supports the efficacy of methotrexate for severe inflammatory skin disease in children

Syed I. Rahman, BA,[a] Elaine Siegfried, MD,[b] Katherine H. Flanagan, MD,[c] and Eric S. Armbrecht, PhD[d]
Saint Louis, Missouri, and Birmingham, Alabama

Background: The methotrexate (MTX) polyglutamate assay has been validated in adults with arthritis.

Objective: We sought to assess clinical response rates and the value of the methotrexate polyglutamate assay in MTX-treated children with inflammatory skin diseases.

Methods: In this retrospective review, 46 MTX-treated children with a diagnosis of atopic dermatitis, psoriasis, or psoriasis-eczema overlap were serially assessed with the methotrexate polyglutamate assay.

Results: In all, 38 children (83%) achieved good to excellent response: 27 (59%) within 12 weeks and 11 (24%) after dose-adjustment. Good to excellent responses were highest for psoriasis/overlap: 15 of 16 (94%), compared with 23 of 30 (77%) with atopic dermatitis. Mean maximum polyglutamate levels were 31.5 nmol/L for responders versus 18.1 nmol/L for nonresponders (P = .035). This difference was also significant for the subset with atopic dermatitis, but not for those with psoriasis/overlap. After dose modification, late responders ultimately achieved a significantly higher mean maximum methotrexate polyglutamate assay (41.9 nmol/L) compared with nonresponders (P = .002).

Limitations: Retrospective design and small sample size were limitations.

Conclusions: MTX is an effective treatment for the majority of children with inflammatory skin diseases, but a subset requires dose modification to achieve good to excellent response. Methotrexate polyglutamate assay levels reflect response to treatment, but are most useful to support dose modification among children who fail to respond within 12 weeks. (J Am Acad Dermatol 2014;70:252-6.)

Key words: atopic dermatitis; methotrexate; methotrexate polyglutamate assay; overlap; pediatric/children; psoriasis.

Methotrexate (MTX) is a convenient, inexpensive, versatile, and well-tolerated drug used for more than 50 years to treat a wide variety of conditions in adults and children, including inflammatory skin diseases. However, there are limited data on the safety and efficacy of MTX in children with severe psoriasis or atopic dermatitis (AD) and even less information on age-related pharmacokinetics, ideal starting dose, optimal route of administration, or approach to dose adjustment.[1] A standardized biomarker to assist with optimal dosing and administration could enhance the use of this time-honored and cost-effective drug.

Abbreviations used:

AD: atopic dermatitis
MTX: methotrexate

From the Saint Louis University School of Medicine[a]; Department of Pediatrics, Division of Dermatology, SSM Cardinal Glennon Children's Medical Center, Saint Louis[b]; Dermatology and Laser of Alabama[c]; and Saint Louis University Center for Outcomes Research.[d]

Funding sources: None.
Conflicts of interest: None declared.
A portion of this data was presented at the Third International Conference on Clinical and Experimental Dermatology in Northbrook, IL, on April 15, 2013.
Accepted for publication October 1, 2013.

Reprints not available from the authors.
Correspondence to: Elaine Siegfried, MD, Department of Pediatrics, Division of Dermatology, SSM Cardinal Glennon Children's Medical Center, 1465 S Grand Blvd, Saint Louis, MO 63104. E-mail: esiegfri@slu.edu.

Published online December 10, 2013.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2013.10.001

MTX is a pro-drug requiring enzymatic conversion through sequential addition of glutamic acid residues to form MTX polyglutamates.[2] The methotrexate polyglutamate assay (AvisePG, Exagen Diagnostics Inc, Albuquerque, NM) measures the predominant triglutamate moiety and was developed as a pharmacogenetic tool to help define an optimal therapeutic range.[3] It has been studied in adults treated with MTX for rheumatoid arthritis, Crohn's disease, and most recently psoriasis.[4,5] This study was undertaken to evaluate the efficacy of MTX and the usefulness of the methotrexate polyglutamate assay in treating severe inflammatory skin disease in children.

CAPSULE SUMMARY

- Methotrexate is effective for children with a diagnosis of atopic dermatitis, psoriasis, or psoriasis-eczema overlap.
- Response to 0.5 mg/kg/wk is achieved within 12 weeks in the majority, but a subset requires dose modification.
- Methotrexate polyglutamate assay reflects treatment efficacy, but is most useful for dose modification among children who fail to respond within 12 weeks.

METHODS

A retrospective chart review was performed after approval by the Saint Louis University Institutional Review Board.

Subjects

The cohort of subjects was retrospectively identified from among all patients treated at the SSM Cardinal Glennon Children's Medical Center Dermatology Clinics between October 2007 and May 2011. Included were children with a diagnosis of AD, psoriasis, or psoriasis-eczema overlap treated with MTX for a minimum of 12 weeks. Children were considered eligible for MTX if they failed aggressive topical treatment and had no history of frequent infections, including more than 6 episodes of otitis media within the first 2 years of life, recurrent group A streptococcal pharyngitis, sinusitis, or recurrent cutaneous herpes simplex. Standard initial dosing was rounded to 0.5 mg/kg administered by mouth weekly as either 2.5-mg tablets or liquid (2.5 mg/0.1-mL injectable solution) to a maximum starting dose of 15 mg. Methotrexate polyglutamate assay levels were initially assessed after 12 weeks of treatment and 8 weeks after every dose adjustment. Dose increase or change to subcutaneous injection was recommended after 12 weeks for patients who failed to respond to initial therapy.

Clinical evaluation

The following variables were abstracted from the patient medical records and used for data analysis: dermatologic diagnosis (AD, psoriasis, overlap), initial and subsequent MTX dose, methotrexate polyglutamate assay values, skin examination, and clinical response.

The severity of each patient's skin condition was qualitatively recorded at every visit, and subsequently quantified using a Physician Global Assessment to reflect disease severity with the following scale: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe.

Methotrexate polyglutamate assay

MTX is metabolized intracellularly via sequential, enzymatically controlled, covalent attachment and removal of glutamic residues. At steady state, the active metabolites include a pharmacogenetically determined admixture of polyglutamated molecules with glutamate tails of different lengths ranging from 1 to 7 residues. The triglutamate species predominates. The methotrexate polyglutamate assay test measures the concentration of this predominant metabolite in red blood cells by means of high-performance liquid chromatography by fluorescent analysis.[3]

Statistical analysis

Mean methotrexate polyglutamate assay values were separately assessed by subgroup, based on clinical diagnosis and therapeutic response. Diagnostic subgroups were: AD and psoriasis plus overlap. For purposes of statistical analysis, children with clinical features suggestive of overlap were grouped with those of psoriasis because children with overlap share more clinical features with those who have psoriasis than AD including approach to treatment and therapeutic responses. In addition, dermatitis triggers psoriasis via Koebner phenomenon, but psoriasis does not trigger dermatitis.[6] To quantify response to treatment, patients who had a 2-point or more improvement were considered responders, whereas those who never achieved this degree of improvement were nonresponders. Among responders, patients were classified as early responders if they achieved a 2 point or more improvement within the first 12 weeks of treatment. Those who responded after dose modification subsequent to the initial 12-week

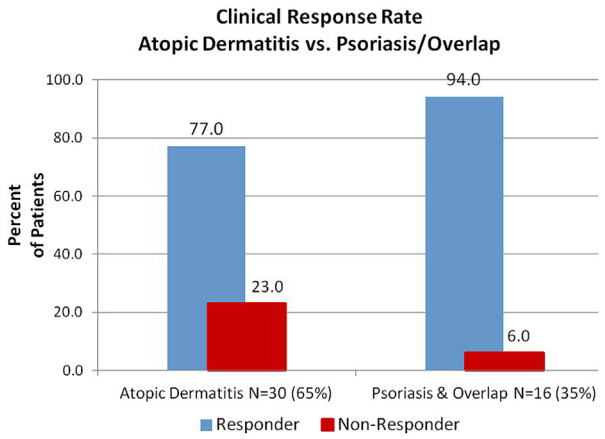

Fig 1. The response rate was high in both subgroups of children treated with methotrexate, but the proportion of responders was highest in children with clinical features of psoriasis.

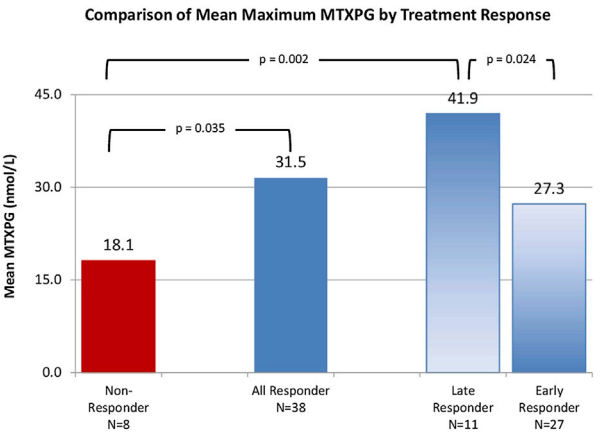

Fig 2. Among the entire cohort, the maximum methotrexate polyglutamate assay (*MTXPG*) level was significantly higher among 38 children who responded to treatment, compared with 8 children who failed to respond. The maximum methotrexate polyglutamate assay level did not reflect treatment efficacy among the majority of responders who improved within 12 weeks of treatment, but it did help guide dose modification for children who initially failed to achieve a 2-point or more clinical improvement.

methotrexate polyglutamate assay were considered late responders.

All methotrexate polyglutamate assay measurements were based on maximum observed change from baseline. Statistical comparisons were made using a 2-tailed *t* test and z-test with alpha 0.05 as the threshold for determining statistical significance.

RESULTS

The 46 children in our cohort had a median age of 8 years (range, 2-17). The largest subgroup had AD (n = 30). The remainder had either psoriasis or overlap (n = 16). The average starting dose was 0.48 mg/kg/wk for children who weighed up to 30 kg. The maximum weekly dose of 15 mg yielded an average starting dose of 0.33 mg/kg for children over 30 kg. The mean duration of treatment was 363 days.

Of the entire 46 patient cohort, 38 (83%) were responders and 8 (17%) were nonresponders. The highest response rate (94%) was among the subset with features of psoriasis, either classic psoriasis or overlap (Fig 1). Mean maximum methotrexate polyglutamate assay levels were significantly higher among responders (31.5 nmol/L ± 16.8) compared with nonresponders (18.1 nmol/L ± 8.4; P = .035) (Fig 2).

Among the 38 responders, the mean maximum methotrexate polyglutamate assay level for 27 children who had a 2-point or more clinical improvement within 12 weeks was 27.3 nmol/L ± 15.1. These early responders represented the majority of all responders (71%; 59% of the total cohort). For the 11 late responders, dose modification resulted in a significantly higher mean maximum methotrexate polyglutamate assay (41.9 nmol/L ± 17; P = .0732) (Fig 2). All of these late responders achieved a

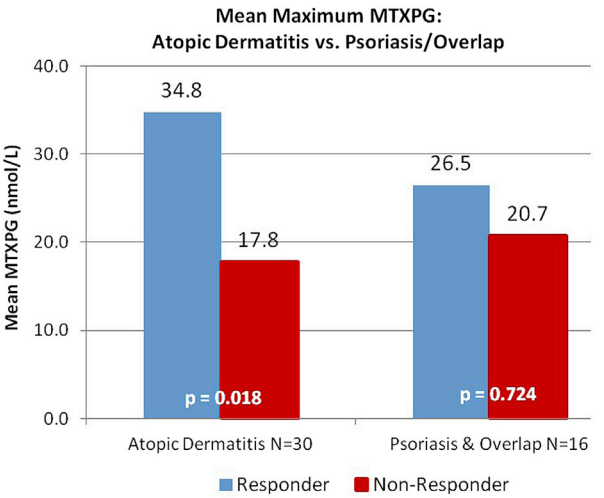

Fig 3. The average mean maximum methotrexate polyglutamate assay (*MTXPG*) for the 30 children with AD correlated with clinical response, but for the 16 patients with features that included psoriasis, there was no difference in the average mean maximum methotrexate polyglutamate assay for responders compared with nonresponders.

methotrexate polyglutamate assay level greater than 30 nmol/L.

The mean maximum methotrexate polyglutamate assay for the 30 children with AD also correlated with clinical improvement: 34.8 nmol/L ± 17.0 for responders and 17.8 nmol/L ± 9.0 for nonresponders

(P = .018). But for the 16 patients with features that included psoriasis, there was no difference in the mean maximum methotrexate polyglutamate assay for responders compared with nonresponders (26.5 ± 15.8 and 20.7 nmol/L, respectively; P = .724) (Fig 3).

None of the patients in the cohort experienced adverse effects necessitating decrease in dose or discontinuation of the medication.

DISCUSSION

MTX is among the choices considered standard of care for systemic treatment of severe inflammatory skin disease.[1] Of children in our series, 60% responded within 3 months of treatment initiation. The overall clinical response rate was 83%, including the subset of late responders who required dose adjustment. Response to therapy was highest, at 94%, among the smaller subset of children whose disease included features of psoriasis. This confirms a widely held clinical impression that MTX is a useful treatment for inflammatory skin disease in children, and underscores the relatively prolonged time to response in some patients. At low doses, MTX is considered cytostatic, rather than myelosuppressive.[7] The drug is also readily available, inexpensive, and convenient, so recognition of the expected time to response and the need for dose adjustment in a subset of patients are important adjuncts for successful management with this useful treatment.

Psoriasis-eczema overlap is an underrecognized but not uncommon condition, first described in 2005.[8] Affected children have clinical features of both disorders, but are often assumed to have the more common AD.[6] For optimal treatment, it is important to appreciate the sometimes subtle features of psoriasis. These include nail pits, posterior auricular scale, and sharply circumscribed nummular lesions with predilection for sites of friction. The Koebner phenomenon is a common trigger for psoriasis, and dermatitis is a source of koebnerization in children with overlap. Skin disease among children with psoriasis or overlap does not respond as well to topical corticosteroid monotherapy and tends to relapse with discontinuation. This study supports the efficacy of MTX as a versatile option for children with all 3 inflammatory skin diseases, but children with psoriasis and overlap may respond even better to MTX than children with AD.

The methotrexate polyglutamate assay level best reflected clinical response in the largest subgroup of children who had AD. Because response is slow, occurring within 3 months for the majority of children, but more than 6 months for a significant minority, the methotrexate polyglutamate assay was most clinically useful in allowing dose adjustment among patients who were slow to respond to initial therapy. Our data suggest that the test is superfluous for those who respond within 12 weeks. Although our cohort was too small for subset analysis, methotrexate polyglutamate assay levels increased after an increased oral dose in some patients. In others, the methotrexate polyglutamate assay level increased after change from oral to subcutaneous administration at the same dosage. Therefore, for patients who fail to improve within 12 weeks after starting treatment, a methotrexate polyglutamate assay level less than 30 nmol/L suggests that increasing the dose or changing to a subcutaneous route of administration is likely to yield an improved response. The average maximum methotrexate polyglutamate assay level of 42 nmol/L among late responding children in our cohort is somewhat less than the therapeutic level of more than 60 nmol/L that has been defined for adults with rheumatoid arthritis.[4]

Interpretation of the methotrexate polyglutamate assay may be biased by pharmacogenetic variation. In some patients, MTX may be metabolized to higher levels of polyglutamation at steady state, with quadra- or tetra-glutamated species predominating. These may be responders with relatively low levels of the methotrexate polyglutamate assay. The common methotrexate folate reductase gene is a possible candidate governing this variation.[9]

This study was limited by sample size and retrospective design, but the data suggest that additional investigation could optimize MTX treatment in children with severe inflammatory skin disease, including analysis of dosing based on weight versus body surface area, and weight-route of administration.

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