

Treatment of severe pediatric atopic dermatitis with methotrexate: A retrospective review

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Abstract

Background/Objectives: Severe atopic dermatitis (AD) may require systemic immunomodulatory agents to control symptoms. A lack of evidence and guidelines for systemic AD therapy in children has led to variability in agents selected and uncertainty in their comparative efficacy and safety. Evaluation of the efficacy of methotrexate in children with severe AD was performed.

Methods: We performed a retrospective chart review of 55 pediatric patients seen at Children's Hospital of Philadelphia that measured improvement using the Investigator's Global Assessment (IGA), a scale that rates AD symptoms from 0 to 5.

Results: About 76% of patients showed improvement with methotrexate. Mean baseline IGA of all patients was 4.18. After 6-9 months of treatment, this improved to 2.94. There was additional improvement to a mean IGA score of 2.39 after 12-15 months of treatment. At the final visit before each patient stopped methotrexate, the mean IGA score was 2.71. Approximately 50% of patients experienced minor side effects with gastrointestinal side effects the most common.

Conclusions: In a diverse patient population, safety and efficacy of methotrexate was demonstrated. Significant improvement in IGA was noted for the majority after 6-9 months of therapy with further improvement when continuing treatment to 12-15 months. Methotrexate remains an important option for long-term symptom control with a favorable side effect profile and low cost.

KEYWORDS

atopic dermatitis, systemic therapy

1 | INTRODUCTION

Atopic dermatitis (AD) is the most common pediatric inflammatory skin disorder in industrialized countries.¹ Severe AD has a significant impact on quality of life, comparable to other chronic conditions of childhood like cystic fibrosis.² While many cases respond to topical therapy, refractory cases may require systemic immunomodulatory agents to control symptoms. A lack of guidelines for systemic AD therapy in children has led to variability in agents selected and uncertainty in their comparative efficacy and safety.³ The most common systemic agents for AD treatment include cyclosporine,

azathioprine, and methotrexate. However, there are concerning adverse effects associated with long-term use of cyclosporine and azathioprine.⁴ Thus, methotrexate may be a preferred option for the treatment of pediatric AD.

Small studies have evaluated the efficacy of methotrexate in children with severe AD. A 2012 randomized controlled trial comparing methotrexate and cyclosporine found no difference between agents in symptom improvement or tolerance, though patients treated with methotrexate experienced longer remissions.⁵ A retrospective chart review of 31 children found methotrexate to be "effective" or "very effective" in 75% of patients, based on subjective comments in the notes.⁶ Finally,

a retrospective review of 47 children with severe AD by Dvorakova et al saw significant symptom improvement measured by the Investigator's Global Assessment (IGA), a scale that rates AD symptoms from 0 to 5.⁷

We sought to compare the results in the Dvorakova et al population to those seen in our dermatology clinic at the Children's Hospital of Philadelphia, a tertiary care center that serves a diverse urban population. Though methotrexate in pediatric AD has been assessed in small studies, more evidence is needed to strengthen treatment guidelines for the use of this agent in children.

2 | METHODS

A retrospective review was performed of all patients initiating methotrexate therapy for severe AD between December 2008 and January 2018 at the Children's Hospital of Philadelphia. Institutional Review Board approval was obtained prior to this review. Demographic data for each patient including sex, race/ethnicity, Fitzpatrick skin type, comorbidities, age at AD onset, and age at methotrexate commencement were recorded. Previous hospitalizations and emergency department visits for AD flares, as well as previous systemic treatments for AD, were documented.

Details of treatment course were noted including the formulation, starting dose and highest dose reached (mg/kg), duration at these doses, total duration of therapy, and concurrent topical therapies used. In addition, the number of skin infections acquired while on methotrexate and their etiological agents were determined, if applicable.

To assess outcomes, the overall effect (improved/not improved), time to clinical improvement, and specific symptomatic changes were documented. Initial improvement was noted when there was documentation by the provider, reduced area of involvement on exam, or reports of reduced pruritus by the patient. The severity of AD was evaluated through retroactive assignment of an IGA score based on qualitative descriptions in the notes, per the scale used by Eichenfield et al.^{8,9} IGA scores were retrospectively calculated at treatment commencement, 6-9 months, 12-15 months, and the final visit before stopping methotrexate. Analysis was performed by reviewing wording of the physical exam (erythema, papules, crusting, oozing) and final physician assessment (clear, mild, moderate, severe). After training, IGA scaling was conducted by a single investigator (K.A.) with re-review of selected charts by senior author (L.C.S.). With this scale, 0 corresponded to clear, 1 was almost clear, 2 was mild disease, 3 was moderate disease, 4 was severe disease, and 5 was very severe disease.⁹ Adverse effects and lab abnormalities during the treatment course were noted. Finally, it was determined whether patients were still on methotrexate at the time of review, and if not, the therapy chosen after completion was recorded.

Means and standard deviations of the IGA scores were calculated at each time point. To analyze the significance of the overall difference in these values over time, The Friedman test, a nonparametric alternative to the One-Way Repeated Measures ANOVA, was used. To determine the significance of the difference in IGA scores between

commencement and each subsequent time point, post hoc analyses with Wilcoxon signed-rank tests were conducted with a Bonferroni correction applied, resulting in a significance level set at $P < 0.017$. In addition, patients were divided into two groups based on whether or not they improved on methotrexate. T tests and chi-square, or non-parametric equivalent, analyses were employed to determine if these two groups differed significantly in their demographic or treatment characteristics. P -values < 0.05 were considered statistically significant. Finally, in the characteristics that were determined to have a significant association with improvement status, logistic regression was applied to determine the impact of that relationship.

3 | RESULTS

3.1 | Demographics

Fifty-five patients met criteria for inclusion. Demographic characteristics and disease history of these patients are summarized in Table 1.

3.2 | Treatment course characteristics

Mean age at treatment commencement was 10.6 years (range 3.0-19.5 years). The patients exhibited severe, longstanding disease at initiation, with 43 patients (78.2%) having a disease duration greater than 5 years. Five patients had undergone treatment with methotrexate in the past and reinitiated the treatment upon disease relapse; for this review, their most recent methotrexate course was used for data collection. History of disease and treatment are summarized in Table 2.

Throughout treatment, 38 patients (69.1%) took only oral methotrexate, two patients (3.6%) used only subcutaneous injections, and 15 patients (27.3%) used both formulations. Patients in the latter group switched from the oral to subcutaneous form to mitigate side effects or increase bioavailability for symptom improvement. Mean duration of treatment was 15.3 months. Dosage and other treatment characteristics are summarized in Table 2.

3.3 | Efficacy

42 patients (76.4%) showed improvement with methotrexate and 13 patients (23.6%) showed no significant improvement, per provider documentation. The most frequent change was decreased area of involvement (40 of 42 improved patients). In the 42 improved patients, most (39) patients saw appreciable improvement in less than 2 months. Other treatment outcomes are detailed in Table 3.

Mean baseline IGA of all patients was 4.2. After 6-9 months of treatment, this improved to 2.9. There was additional improvement to a mean IGA score of 2.4 after 12-15 months of treatment. At the final visit before each patient stopped methotrexate, the mean IGA score was 2.7 (Table 3). The Friedman test showed a statistically significant difference in IGA values over time ($\chi^2(3) = 86.6, P < 0.0001$). Post hoc analysis with Wilcoxon signed-rank tests showed significant reductions

TABLE 1 Patient demographics and disease characteristics

Characteristic	Value
Sex, n (%)	
Female	30 (54.5)
Male	25 (45.5)
Fitzpatrick skin type, n (%) ^a	
I	9 (19.1)
II	19 (40.4)
III	2 (4.3)
IV	11 (23.4)
V	6 (12.8)
Race/Ethnicity, n (%)	
American Indian	1 (1.8)
Asian	3 (5.5)
Black or African American	11 (20.0)
Caucasian	27 (49.1)
Hispanic/Latino	2 (3.6)
Indian	3 (5.5)
Other	8 (14.5)
Age of AD onset, mean (range), y	1.3 (0.3–13.8)
Comorbidities, n (%)	
Allergic Rhinitis	43 (78.2)
Alopecia areata	2 (3.6)
Anxiety	6 (10.9)
Asthma	38 (69.1)
Contact allergies	25 (45.5)
Eosinophilic esophagitis	6 (10.9)
Food allergies	37 (67.3)
Ichthyosis vulgaris	1 (1.8)
Plantar keratoderma	1 (1.8)
Vitiligo	2 (3.6)

^aEight patients did not have a Fitzpatrick skin type listed in their records.

in IGA values between commencement and each time point: 1.3 after 6–9 months, 1.8 after 12–15 months, and 1.5 between commencement and final visit (all P -values < 0.0001). Of note, 17 patients had treatment courses shorter than 12 months, 8 of whom had courses less than 6 months. These patients, regardless of their treatment duration, were included in the final visit IGA analysis, but were unable to be included at the 12–15 month and 6–9 month analyses, respectively.

Eight patients were still undergoing treatment with methotrexate at the time of review. Of the patients whose post-methotrexate therapy was able to be determined, 27 patients transitioned to topical therapy and 8 patients switched to another systemic agent. These data are summarized in Table 3.

T tests and chi-square analyses were used to identify differences between improved and unimproved groups in skin type,

TABLE 2 Atopic dermatitis (AD) history and treatment characteristics (N = 55)

Characteristic	Value
Age at MTX commencement, mean (range)	10.6 (3.0–19.5)
Duration of disease at commencement, n (%)	
1–2 y	4 (7.3)
3–4 y	8 (14.5)
> 5 y	43 (78.2)
Prior treatments, n (%)	
Azathioprine	3 (5.5)
Cyclosporine	6 (10.9)
Mycophenolate	3 (5.5)
Oral Methotrexate	5 (9.1)
UVB Therapy	21 (38.2)
Concurrent treatments, n (%)	
Topical Steroids	51 (92.7)
Nonsteroidal topicals	29 (52.7)
Other	2 (3.6)
#Patients previously admitted for AD, n (%)	18 (32.7)
#Patients with prior ED visits, n (%)	21 (38.2)
MTX formulation, n (%)	
Oral	38 (69.1)
Subcutaneous	2 (3.6)
Both	15 (27.3)
Mean starting dose, mg/kg	0.37 (0.12–0.73)
Mean duration at initial dose, months	4.5 (1.0–24.5)
Mean highest dose reached, oral, mg/kg	0.45 (0.12–1.00)
Mean highest dose reach, subcutaneous, mg/kg	0.50 (0.22–0.77)
Total treatment duration, months	15.3 (3.0–39.0)

comorbidities, age at commencement, highest dose reached, total treatment duration, and number of skin infections acquired. The highest oral dose reached was significantly greater in the unimproved group (mean 0.56 mg/kg), compared to the improved group (mean 0.41 mg/kg; $t = -2.46$, $P = 0.019$). Logistic regression showed for every 0.01 mg/kg increase in highest dose reached, the odds of improvement decreased by a factor of 0.01 (OR 0.01 (0, 0.70), $P = 0.034$). Total duration of treatment was significantly higher in the improved group (mean 17.4 months), compared to the unimproved group (mean 8.4 months; $t = 3.84$, $P < 0.001$). Logistic regression showed that for every 1 month increase in treatment duration, the odds of improvement increased by a factor of 1.28 (OR = 1.28, (1.10, 1.48) $P = 0.002$).

3.4 | Safety and tolerability

Twenty-eight patients (50.9%) experienced at least one adverse effect during methotrexate therapy. The most common was GI discomfort and nausea, experienced by 17 patients (30.9%; Table 4).

TABLE 3 Treatment outcomes (N = 55)

Factor	Value
Mean IGA at commencement, n = 55	4.2 ± 0.6 (3-5)
Mean IGA at 6-9 mo, n = 47	2.9 ± 1.1 (0-5)
ΔIGA from commencement to 6-9 mo	1.3 ± 1.0
Mean IGA at 12-15 mo, n = 38	2.4 ± 1.2 (0-5)
ΔIGA from commencement to 12-15 mo	1.8 ± 1.2
Final IGA, n = 55	2.7 ± 1.3 (0-5)
ΔIGA from commencement to final visit	1.5 ± 1.2
Months to improvement, n (%)	
< 2 mo	39 (70.9)
3-4 mo	2 (3.6)
5-6 mo	1 (1.8)
Specific effect observed	
Decreased area of involvement	40 (72.7)
Decreased topical steroid use	36 (65.5)
Decreased pruritus	36 (65.5)
Reduced erythema	30 (54.5)
Improved lichenification	29 (52.7)
Reduced edema/papulation	26 (47.3)
Decreased excoriations	20 (36.4)
Treatment chosen after methotrexate, n (%)	
Azathioprine	5 (9.1)
Cyclosporine	2 (3.6)
Mycophenolate	1 (1.8)
Topical therapy	27 (49.1)
Other	12 (21.8)

Seven patients had a bloodwork abnormality resulting in either lowering of dose (3 patients) or discontinuation (1 patient). Twenty-six patients acquired at least one skin infection while taking methotrexate. Safety and tolerability findings are summarized in Table 4.

4 | DISCUSSION

The American Academy for Dermatology recommends immunomodulatory agents for treatment of refractory AD, but there remains a lack of evidence and dosing guidelines for children.³ This study provides evidence for the safety and efficacy of methotrexate in treating pediatric AD. Much of current practice is based on the use of methotrexate in treating adult AD or other conditions. For this reason, we recreated the Dvorakova et al study in our patients to further characterize the use of methotrexate for pediatric AD.

There are several options in selecting an immunomodulatory agent to treat AD. Cyclosporine works quickly, but there is often a rapid relapse in symptoms upon cessation. Furthermore, there is a risk of hypertension and renal damage with long-term use.¹⁰ Azathioprine has a slower onset but longer duration of action. However, its malignancy

TABLE 4 Methotrexate safety and tolerability (N = 55)

Factor	Value
Adverse effects, n (%)	
GI discomfort/Nausea	17 (30.9)
Fatigue	14 (25.5)
Headaches	9 (16.4)
Blurry vision	3 (5.5)
Mouth sores	3 (5.5)
Lab abnormalities, n (%)	
Transient elevated transaminases	5 (9.1)
Low hematocrit and hemoglobin	2 (3.6)
Skin infections, n (%)	
Cellulitis	2 (3.6)
Eczema herpeticum	1 (1.8)
Folliculitis	1 (1.8)
Molluscum	8 (14.5)
Methicillin-sensitive <i>Staphylococcus aureus</i> Superinfection	16 (29.1)
Methicillin-resistant <i>Staphylococcus aureus</i> Superinfection	6 (10.9)
Ocular herpes simplex infection	1 (1.8)
Ringworm	1 (1.8)
Verruca vulgaris	1 (1.8)

black box warning is worrisome for prolonged use in children.¹⁰ Dupilumab, an antibody targeting interleukin-4 receptors, has shown promising results in adult AD. However, it is not U.S. Food and Drug Administration approved for use in children and its high cost will likely make it a secondary option for those who failed other agents.¹¹ Our results suggest methotrexate is a safe, reliable alternative to these therapies for long-term AD symptom control.

This patient population differed from the Dvorakova et al population in terms of demographics. Our patients were more diverse in Fitzpatrick skin type and race, consistent with the patient population in Philadelphia. In addition, our patients had more comorbidities at baseline (Table 1). However, AD history in our patients closely mirrored that of the Dvorakova et al review regarding age of onset, duration, and previous hospitalizations. Treatment practices were similar, although our group had more patients using the injectable formulation and underwent more frequent dose adjustments to achieve symptom remission.

Higher oral doses were reached in the patients who did not improve, reflecting the practice of increasing dose to control symptoms in refractory cases. This finding may suggest that patients who do not respond to methotrexate are "resistant" to even the highest doses and may be better candidates for a different medication. In addition, the improved group had a longer mean duration of treatment. This is likely because patients in the unimproved group switched to a different agent early in their treatment to seek better results.

Like Dvorakova et al, we saw significant improvement in IGA score after 6–9 months, which was further improved when continuing treatment to 12–15 months. Based on IGA scores, our patients had severe disease at the start of treatment, and the average patient had mild to moderate disease after completion. The time to effect was also similar, with Dvorakova et al having an average of 11.3 weeks, and 39 of our 42 improved patients requiring less than 2 months to see improvement. An important difference between studies is that almost a quarter of our patients did not improve on methotrexate, whereas only three of their patients were unsuccessful.

Our review is limited by the retroactive application of IGA scores. Due to the nature of this scale, it would be ideal to have this assessment made in person and recorded at each visit. The consistency of our results with those of Dvorakova et al is encouraging for the use of the IGA scale in reliably illustrating tangible improvement of AD symptoms. In the future, an IGA score or similar metric can be assigned at each visit to track clinical improvement in real time.

Our findings support those of Dvorakova et al that methotrexate is a safe and effective treatment for severe AD. Despite the development of targeted agents like dupilumab as potential treatments of pediatric AD, methotrexate remains an important option for long-term symptom control with a mild side effect profile and low cost.

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