Pharmacology and therapeutics

Methotrexate for treatment of atopic dermatitis in children and adolescents

Maneka Deo, MBChB, Anthony Yung, MBChB, FRACP, CCST, Sarah Hill, MBChB, FRACP, and Marius Rademaker, FRCP, FRACP, DM

Department of Dermatology, Waikato Hospital, Hamilton, New Zealand

Correspondence
Maneka Deo
Department of Dermatology
Waikato Hospital
Hamilton
New Zealand
E-mail: manekad@adhb.govt.nz

Abstract

Background Low-dose methotrexate is becoming established as a second-line treatment for atopic eczema in the adult population, but there has been a paucity of data to support its use for this indication in the pediatric population.

Methods A retrospective review was undertaken of patients aged 18 years and under started on methotrexate between January 2005 and April 2010, at a hospital-based dermatology department in New Zealand.

Results Thirty-one patients (17 females, mean age 10 years, range 3–18 years) were reviewed. Methotrexate was found to be effective or very effective in 75% and ineffective in 25%. The mean duration of treatment for those who responded to methotrexate was 14 months (range 2–38 months), 74% of patients were still on treatment at the time of last review. The most common adverse effect was minor nausea in four patients (14%) and non-significant elevation of liver enzymes (four patients). No serious adverse effects were noted.

Conclusion In our experience, methotrexate has a good safety/tolerability profile when used in low dose for the treatment of atopic dermatitis in children and adolescents and appears to be effective. Formal comparative studies are needed.

Introduction

Atopic dermatitis is a common inflammatory skin disease in the pediatric and adult population. It is a major cause of morbidity, with effects on growth and development, sleep quality, school attendance, and psychosocial well-being of the affected individual as well as their family.1 The reported prevalence of the condition ranges from 0.2 to 24.6% in the pediatric age group with significant geographic variation.2 There is a relatively high prevalence of atopic dermatitis in New Zealand, with reported figures of 15% in those aged 6–7 years and 8.8% in those aged 13–14 years.3

The mainstay of treatment for atopic dermatitis in childhood remains topical corticosteroids, with topical calcineurin inhibitors and phototherapy1 being commonly used alternatives. Systemic treatments are often required in severe eczema, which does not respond adequately to other treatments.4 Traditionally used systemic therapies include cyclosporine and azathioprine; however, side effects can be problematic with these medications, and the necessary blood monitoring can affect adherence, particularly in children and adolescents. Low-dose methotrexate is now fairly well established as a second-line treatment for atopic eczema in the adult population,5–8 although double-blind placebo-controlled studies are lacking. While methotrexate has well-established safety and efficacy data for use in juvenile rheumatoid arthritis and pediatric Crohn’s disease,9–11 there has been a paucity of data to support its use for atopic eczema in children. Recently, a case series of pediatric patients with discoid eczema reported its efficacy and safety.12

We review our retrospective experience of methotrexate in children and adolescents with atopic dermatitis.

Materials and methods

The clinical records of patients aged 18 years or below who were started on methotrexate between January 2005 and April 2010 at the dermatology department of Waikato Hospital, Hamilton, New Zealand, were reviewed. Demographic details as well as clinical details of the patient’s dermatological disease, previous treatments, and response to methotrexate were analyzed. Data have been recorded prospectively for the purpose of clinical management of individual patients rather than for research/review purposes, so typical clinical trial data...
serology was only performed if clinically indicated. Liver enzymes, and renal function. Chest x-ray and hepatitis was decreased to every six months if parameters had been normal, every three months thereafter. The frequency of testing methotrexate. Blood monitoring was carried out at (5 mg twice weekly) was given on separate days to the 15 mg weekly for those aged 11 years and over. Folic acid 0 with atopic dermatitis was 5 mg once weekly for patients aged – 5 years, 10 mg once weekly for those aged 6–10 years, and 15 mg weekly for those aged 11 years and over. Folic acid (5 mg twice weekly) was given on separate days to the methotrexate. Blood monitoring was carried out at commencement of treatment and if baseline testing was normal, every three months thereafter. The frequency of testing was decreased to every six months if parameters had been stable. Routine blood monitoring included complete blood count, liver enzymes, and renal function. Chest x-ray and hepatitis serology was only performed if clinically indicated. Baseline characteristics can be seen in Table 1.

Results

Thirty-one children (17 female, 14 male) were started on methotrexate during the review period. All had widespread severe atopic eczema. The average age of starting treatment was 10 years (range 3–18 years). The median length of treatment was 9.5 months (range 2–38 months). All patients had previous treatment with topical steroids with half the patients having had previous phototherapy (narrowband ultraviolet B) with limited success. An extended course of prednisone had been given previously in nine patients (29%) and an extended course of antibiotics (usually 3 months or longer) in 14 patients (45%). One patient (3%) had a previous trial of azathioprine. The median starting dose was 5 mg weekly for patients aged 0–5 years and 10 mg weekly for the 6–10 years, 11–14 years, and 15–18 years age groups. The median treatment dose was 7.5 mg weekly for those aged 0–5 years, 10 mg weekly for the 6–10 years and 11–14 year age groups, and 15 mg weekly for those 15–18 years.

In one patient, treatment was discontinued after only one dose due to change in the decision of the family. Two patients were lost to follow-up – one shortly after initiation of treatment, the second a year after methotrexate initiation. Methotrexate was found to be effective or very effective in 75% of the 28 patients for whom there was adequate follow-up data and ineffective in 25%. This was based on the overall impression of the patient/parent and clinician at clinic review. Objective SCORAD measurements were only available in nine patients: the median pretreatment SCORAD of 50 (range of 40–71) fell to 34 (range of 0–48). Topical corticosteroid use was reduced significantly in responders with most having long periods (months) during which almost no topical corticosteroids were required.

Clinical improvement was noted within 8–12 weeks of starting methotrexate. Three children had acute flares of their atopic eczema in the first six months of treatment with methotrexate. These were managed by short course potent topical corticosteroids, systemic antibiotics, or systemic steroids. The mean duration of treatment in those for whom methotrexate was ineffective, and therefore stopped, was six months (range 3–9 months). The mean duration of treatment for those who responded to methotrexate was 14 months (range 2–38 months).

Three patients stopped methotrexate temporarily during the study period; of these, one was a 3-year-old child in whom there was difficulty administering the oral formulation, but subcutaneous methotrexate was used with excellent effect. One patient, whose eczema had settled after 12 months of methotrexate, had a trial of treatment cessation but relapsed within one month. In the third child, methotrexate was stopped one month after commencement due to (pre-existing) infected eczema. Treatment was restarted successfully a few months later but was discontinued in two responders, one of whom lost response after 11 months (this patient was subsequently treated with azathioprine). The second child was initially unresponsive to methotrexate but later responded to combination treatment of methotrexate and azathioprine. The most common adverse effects were minor nausea, reported on at least one occasion in four patients (14%) and non-clinically significant elevation of the liver

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>0–5 years</td>
</tr>
<tr>
<td>6–10 years</td>
</tr>
<tr>
<td>≥11 years</td>
</tr>
<tr>
<td><strong>Previous treatment</strong></td>
</tr>
<tr>
<td>Topical treatment</td>
</tr>
<tr>
<td>Phototherapy</td>
</tr>
<tr>
<td>Extended course oral corticosteroids</td>
</tr>
<tr>
<td>Extended course oral antibiotics</td>
</tr>
<tr>
<td>Other systemic treatment</td>
</tr>
</tbody>
</table>
enzymes (four patients, 14%). These were all mild, transient phenomena, which did not preclude continuation of treatment. Nocytic anemia was found in two patients: in one patient this was an isolated mild decrease in hemoglobin on one occasion, which was normal on subsequent testing; in the second, the anemia was significant and prolonged but was assessed as being due to concomitant treatment with azathioprine. Serious infections occurred in two patients: pyelonephritis and a viral-induced exacerbation of asthma, requiring admission to hospital. Neither was considered related to methotrexate.

In addition to standard monitoring, type III procollagen was measured in 21 patients (68%). These were abnormal in two-thirds of cases (61.8%), reflecting the inaccuracy of this test during growth.13 Transient elastography (FibroscanTM) of the liver was performed in nine patients (29%), and all produced an F0/F1 result, indicating no or minimal fibrosis. No liver biopsies were performed. Baseline hepatitis serology was normal in the third of children who had this test performed. A pretreatment chest x-ray was done in two patients (6.5%) and was normal in both.

At the end of data collection, 23 patients (74%) remained on methotrexate. One of these patients was on combination treatment with azathioprine and methotrexate. Methotrexate had been stopped in six patients (19%). Two were lost to follow-up.

Results can also been seen in Table 2.

### Conclusion

Methotrexate is an inhibitor of purine and pyrimidine synthesis due to its inhibition of dihydrofolate reductase. It therefore reduces cell proliferation. Low-dose methotrexate also acts as an immune modulator through its effects on the adhesion molecules cutaneous lymphocyte-associated antigen and E-selectin. In addition, low-dose methotrexate has been shown to suppress intercellular adhesion molecule-1. Adenosine is implicated in some of these anti-inflammatory effects.3,4,16

There is now a body of literature to support the use of methotrexate for the treatment of atopic dermatitis in adults. Goujon et al.17 reported that 75% of patients with moderate to severe eczema were greatly improved within 4–8 weeks of treatment with low-dose methotrexate. In a prospective study of 12 patients who had previously been on other second-line treatments, an average reduction in disease activity of 52% was found with use of methotrexate in an incremental dose regimen.6 Lyakhovitsky et al.7 reported the results of a retrospective study of 20 adults with moderate to severe atopic eczema resistant to other second-line treatments. Methotrexate was given at a dose of 10–25 mg weekly (with folic acid). Sixteen patients achieved clinical improvement between 2 and 12 weeks. No serious adverse effects occurred during the study period. A randomized study comparing methotrexate with azathioprine for severe atopic dermatitis concluded that both treatments achieved clinically relevant improvement and were safe in the short term.5

A recent case series of 25 children (aged 3–16 years) with refractory discoid eczema treated with low-dose methotrexate (5–15 mg weekly with folic acid) reported clearance or near-clearance of eczema in 76%, with a mean duration of treatment of 10.5 months for those who achieved clearance and 12 months for those who had near-clearance.12 The most common adverse effect reported was nausea in 16%, but no serious adverse events were noted.

Giannini et al.9 reported the results of a randomized controlled trial comparing low- and very low-dose methotrexate with placebo for resistant juvenile rheumatoid arthritis. In the low-dose group (defined as 10 mg/m² body surface area per week), 13% had clinical evidence of toxicity – adverse events that were deemed clinically important and definitely, probably, or possibly related to the study medication. In the very-low-dose group (5 mg/m² body surface area per week), the rate of adverse events was 20%, and in the placebo group the rate of adverse events was 12%. All of these adverse events in the participants receiving methotrexate were classified as mild or moderate. In terms of laboratory evidence of toxicity, 33% of those in the low-dose and 38% in the very low-dose methotrexate group had abnormal results that were felt to be clinically important and possibly, probably, or definitely related to the study medication compared to 12% in the placebo group. The most common laboratory abnormalities noted in patients taking methotrexate were changes in the white cell differential, hematuria, pyuria, and elevated serum transaminases. It was noted that while mild elevations of serum aminotransferase levels were common, elevations reaching more than

### Table 2 Results

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early withdrawal</td>
<td>1/31</td>
<td>3</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2/31</td>
<td>6</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective or very effective</td>
<td>21/28</td>
<td>75</td>
</tr>
<tr>
<td>Not effective</td>
<td>7/28</td>
<td>25</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4/28</td>
<td>14</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>4/28</td>
<td>14</td>
</tr>
<tr>
<td><strong>Treatment at last review</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing</td>
<td>23/31</td>
<td>74</td>
</tr>
<tr>
<td>Stopped</td>
<td>8/31</td>
<td>26</td>
</tr>
</tbody>
</table>
twice the upper limit of normal were less common at 9% in
the low-dose methotrexate group, 5% in the very low-
dose methotrexate group, and 2% in the placebo group.

In a randomized study comparing methotrexate 0.5
mg/kg (and folic acid) with leflunomide for juvenile
rheumatoid arthritis, no serious adverse events were
reported in the methotrexate group, which included 47
children from week 0 to 16 and 37 children from week 16
to 48.18,19 From week 1 to 16, nausea and/or vomiting was
reported in 34% of those in the methotrexate group, head-
ache and nasopharyngeal symptoms were each reported in
23%, increased aminotransferase levels in 9%, and alopeci
in 6%. A retrospective study of 25 patients aged
<18 years with Crohn’s disease who had previously failed
purine analogues were subsequently treated with metho-
trexate (median dose 12.5 mg/m²) along with folic acid
found that nausea was the most common side effect, occurr-
ing in 9%; the next most common adverse event was per-
sistently elevated transaminases in 6.2%.14 No infectious
or hematological complications were reported over a mean
treatment duration of 13.1 ± 8.7 months (range 0.5–
36 months, median 12 months).

In our experience, methotrexate has a good safety tol-
erability profile when used in low dose for treatment of
atopic dermatitis in children and adolescents and has effi-
cacy comparable to that of other systemic agents used for
this condition.18,19 This, along with its weekly dosing
schedule and suitability as a long-term treatment, make it
good choice for treatment of atopic eczema in young
people. The improvement in clinical signs and symptoms
were seen within 2–3 months. We are not able to com-
ment on length of remission, as 74% of patients were still
on treatment.

This study is limited by being retrospective, having no
control group, and most significantly by not using consist-
tent objective measures of improvement. However, it
reflects clinical practice. With the exception of one child,
whose parents changed their minds after the first dose of
methotrexate, none of the other children/caregivers
expressed concerns regarding treatment. A very recent
multicenter study has been published comparing metho-
trexate with cyclosporine in 40 children with atopic
eczema; this demonstrated that methotrexate was effect-
ive and resulted in a longer-lasting remission than
cyclosporine.20

References

1 Kemp AS. Cost of illness of atopic dermatitis in children:
a societal perspective. Pharmacoeconomics 2003; 21:
105–113.
2 Odhiambo JA, Williams HC, Clayton TO, et al., Group
IPTS. Global variations in prevalence of eczema
symptoms in children from ISAAC Phase Three. J Allergy
3 Tan E, Lim D, Rademaker M. Narrowband UVB
phototherapy in children: a New Zealand experience. Austra-
4 Ring J, Alomar A, Bieber T, et al. Guidelines for treat-
mment of atopic eczema (atopic dermatitis) Part II. J
5 Schram ME, Roekevisch E, Leeflang MMG, et al. A
randomized trial of methotrexate versus azathioprine for
severe atopic eczema. J Allergy Clin Immunol 2011; 128:
353–359.
open-label, dose-ranging study of methotrexate for
moderate-to-severe adult atopic eczema. Br J Dermatol
methotrexate treatment for moderate-to-severe atopic
dermatitis in adults. J Eur Acad Dermatol Venereol 2010; 24:
43–49.
8 Zoller I, Ramon M, Bergman R. Low dose
methotrexate therapy is effective in late-onset atopic
dermatitis and idiopathic eczema. Isr Med Assoc J 2008;
10: 413–414.
9 Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate
in resistant juvenile rheumatoid arthritis. Results of the
U.S.A.-U.S.S.R. double-blind, placebo-controlled trial.
The Pediatric Rheumatology Collaborative Study Group
and the Cooperative Childrens Study Group. N Engl J
10 Silverman E, Mouy R, Spiegel L, et al. Leflunomide or
methotrexate for juvenile rheumatoid arthritis. N Engl J
treatment in pediatric Crohn disease patients intolerant
or resistant to purine analogues. J Pediatr Gastroenterol
12 Roberts H, Orchard D. Methotrexate is a safe and
effective treatment for paediatric discoid (nummular)
eczema: a case series of 25 children. Australas J
in serum type III procollagen peptide with age in
healthy subjects and its comparative value in the
assessment of disease activity in children and adults
14 Berends MAM, Snoek J, de Jong EMGJ, et al.
Biochemical and biophysical assessment of MTX-induced
liver fibrosis in psoriasis patients: Fibrotest predicts the
presence and Fibroscan predicts the absence of significant
Methotrexate markedly reduces the expression of
vascular E-selectin, cutaneous lymphocyte-associated
antigen and the numbers of mononuclear leukocytes in


