

Role of methotrexate in severe atopic eczema in children

SCENARIO

EW is a 10-year-old female with severe atopic eczema. She has had frequent flare-ups and multiple secondary infections since 6 months of age. Previous therapy has included prednisolone, aciclovir, flucloxacillin, topical fucibet, emollients and steroids. She currently requires high-dose steroids and symptoms recur when tapering the dose. EW's eczema has a severe impact on her quality of life: she has low self-esteem, struggles with sleep and is bullied at school. You wonder if methotrexate would reduce the severity of EW's eczema.

STRUCTURED CLINICAL QUESTION

In children with severe eczema, does methotrexate reduce the severity of symptoms?

SEARCH STRATEGY

- Search terms: "Methotrexate AND children AND eczema" in the Cochrane Library yielded 1 result, which gave a useful reference, in PubMed yielded 16 results, 3 were useful.
- Search terms: "Methotrexate AND children AND atopic dermatitis" in Cochrane Library yielded 2 results both previously found, in PubMed yielded 19 results, 0 were useful.

COMMENTARY

In children with severe eczema refractory to standard therapy, it is essential to ensure treatment compliance, identify secondary infection, allergic or other triggers and review diagnosis. Despite these conservative measures, a small cohort of children will continue to suffer from severe symptoms and a reduced quality of life. In these patients, the National Institute for Health and Care Excellence (NICE) recommends initiation of phototherapy and/or systemic therapies. Methotrexate (MTX) is currently recommended from review of two clinical studies performed in adults.⁵

The above review identifies that high-quality evidence to support this treatment is still sparse. However, all studies show methotrexate to be an effective treatment in reducing severity of symptoms in childhood eczema.

NICE defines severe eczema as the presence of 'severe signs' and/or a 'severe impact on quality of life'.⁵ Severity is measured by "clinical signs, disease extent, patient symptoms, global assessment of disease activity by the physician, child or parent, quantities or strengths of treatment required and impact of disease on QOL of the child and their family".⁵ Lack of objective severity measurement and varying inclusion/exclusion criteria provide an initial challenge when interpreting the above results.

Second, the review highlights wide variation in dosage, duration of MTX treatment and follow-up. Four different methods of prescription, use of adjuvant treatments and duration/follow-up of treatment can be seen across the studies. Such variation reduces validity of results, and further study is needed to identify the most appropriate regimen.

Each study also used different outcome criteria to assess efficacy of treatment. El-Khalawany *et al*¹ used SCORing Atopic Dermatitis (SCORAD); however, in the remaining studies, outcome measures were highly subjective. This was largely unavoidable due to the retrospective nature of these studies, but a clear defined outcome is essential in further trial development.

Finally, the above studies performed minimal statistical analysis, preventing true significance of results from being identified.

Despite these challenges and the minimal evidence cited by NICE, the TREAT survey confirms that MTX is currently being prescribed for children with severe eczema.⁶ To fully support this treatment and refine the most appropriate dosing schedule, more high-quality evidence using MTX in children is needed. Currently, clinical experience, lack of alternatives, evidence of efficacy (from adult studies)⁷⁻⁹ and safety (from other studies using MTX in paediatric inflammatory conditions)^{4 10-13} underpins treatment—not the high-quality evidence-based practice we should be striving for.

Clinical bottom line

- This review of studies demonstrates methotrexate to be effective in children with eczema. (grade B).
- Current data are not robust and further study with defined outcome measures is needed to establish the most appropriate dose and duration of treatment (grade B).

Table 1

Study	Type of study and patient group	Intervention	Outcome	Key result	Personal comments
El-Khalawany <i>et al</i> ¹	Multicentre RCT unblinded 40 children (8–14 years) with severe AD having failed topical therapy. Exclusion criteria: chronic infection, uncontrolled systemic disease	MTX 7.5 mg/week vs cyclosporine 2.5 mg/kg/day 12-week treatment 12-week follow-up Patients used topical emollients and antihistamines PRN	SCORAD 0, 4, 8 and 12 weeks Adverse effects	Both treatments reduced SCORAD at all time points with no statistical significant difference between them. Mean SCORAD reduction at end of treatment: MTX 26.25, cyclosporine 25.01 (p value 0.93) SCORAD reduction at end of follow-up: MTX 24.90, cyclosporine 21.01 (p value 0.29)	Weaknesses ▶ No intention-to-treat analysis ▶ No power calculation ▶ Not blinded ▶ Trial not registered on trial registry ▶ No drug history for patients/ data on ongoing treatments ▶ Inappropriate dosages: low cyclosporine, MTX not tailored to patients ▶ Short time frame: MTX takes ~2 months to show effect ▶ Cyclosporine has rapid effect —inappropriate to compare these rx? Strengths ▶ 1st RCT of this kind ▶ Good inclusion/exclusion criteria ▶ Follow-up after therapy to assess duration of response ▶ Narrow age range
Deo <i>et al</i> ²	Retrospective review 31 children (3–18 years) with widespread severe atopic eczema	MTX 0–5 years 5 mg, 6–10 10 mg, >11 15 mg Mean duration 9.5 months (2–38 months) Patients had had range of previous therapies: all topical steroids, ~50% phototherapy	Review of subjective comments made on patients notes at each appointment: patient/parents view of condition, sleep improvement, reduction in use of systemic corticosteroids/ calcineurin inhibitors and dermatologists overall opinion	Effective/very effective in 75% Ineffective 25% Reduction in topical steroids and antibiotics in responders	Weaknesses ▶ Retrospective: cannot specify criteria/outcomes, ▶ No control group ▶ Wide range of subjective outcome measures ▶ Varying treatment duration between patients when outcomes measured ▶ No data on time to response ▶ No statistical analysis Strengths ▶ Patient, parent and dermatologist assessment
Rahman <i>et al</i> ³	Retrospective review 46 children (2–17 years) with atopic dermatitis, psoriasis, or psoriasis-eczema whom had previously failed aggressive topical treatment. Exclusion: extensive infection history	MTX 0.5 mg/kg. Minimum duration of 12 weeks (mean 363 days)	Physician Global Assessment to reflect disease severity with the following scale: 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe. Response=improvement ≥ 2 points	83% responded Most common in psoriasis/overlap (94%)	Weaknesses ▶ Retrospective design ▶ Minimal data about patient groups—other medications, duration of treatment, previous therapies. ▶ No data on time or duration of response ▶ Sparse statistical analysis ▶ Inclusion of psoriasis patients Strengths ▶ Dose MTX mg/kg ▶ Long duration of treatment ▶ Defined response definition

Continued

Table 1 Continued

Study	Type of study and patient group	Intervention	Outcome	Key result	Personal comments
Roberts <i>et al</i> ⁴	Retrospective 25 patient case series 25 children (3–16 years) with refractory discoid eczema having failed appropriate first-line therapy. All previously received topical steroids and abx. 6 patients cyclosporine, 3 patients phototherapy, 1 AZT	MTX 5–15 mg/week for 3–30 months with 1–22 months follow-up	Visual assessment: clear, almost clear, ongoing, failed	64% cleared 10.5 months 12% almost cleared 19% relapsed off treatment but were successfully treated by another course MTX	Weaknesses ▲ Discoid eczema is not associated with atopy ▲ Objective outcome: SCORAD not used due to limited surface area in discoid eczema. ▲ Assessors and outcome criteria not described ▲ Varying duration of treatment and follow-up ▲ Adjuvant treatments not specified ▲ No statistics Strengths ▲ Patient follow-up after cessation of rx ▲ Details on time and duration of response ▲ Details on past treatment

AD, atopic dermatitis; AZT, azathioprine; MTX, methotrexate; PRN, as required; RCT, randomised controlled trial; SCORAD, SCORing Atopic Dermatitis.

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