

Methotrexate vs. ciclosporin in the treatment of severe atopic dermatitis in children: a critical appraisal

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Summary

Aim El-Khalawany *et al.* (Eur J Pediatr 2012; **172**: 351–6) aimed to compare the efficacy and safety of methotrexate vs. ciclosporin in the treatment of children with severe atopic eczema.

Setting and design This multicentre, parallel group (ratio 1 : 1), randomized controlled trial was conducted in a secondary care setting in Egypt.

Study exposure Children with severe atopic eczema were randomly assigned to receive either methotrexate (7.5 mg weekly) or ciclosporin (2.5 mg kg⁻¹ daily) for 12 weeks, followed by a 12-week follow-up period.

Outcomes Eczema severity was measured using the SCORing of Atopic Dermatitis (SCORAD) index. The authors also recorded the number of patients on each therapy experiencing adverse effects.

Primary outcome measures The primary outcome was the mean change in SCORAD after 12 weeks of treatment.

Results Forty patients with a mean age of 11.6 ± 1.52 years were included in the trial. At week 12, patients in the methotrexate group had a mean ± SD absolute reduction in SCORAD of 26.25 ± 7.03, compared with 25.02 ± 8.21 in the ciclosporin group (*P* = 0.93). Both drugs were associated with minor adverse effects, none of which necessitated changing the treatment regimen.

Conclusions El-Khalawany *et al.* conclude that both methotrexate and ciclosporin in low doses are clinically effective, relatively safe, and well tolerated as treatments for severe atopic eczema in children.

the U.K. National Health Service. Although the vast majority of cases may be managed in the primary care setting, some 2% of children have severe disease refractory to topical treatments or ultraviolet therapy alone.² These patients require an individualized approach via specialist input, particularly for the use of systemic immunosuppressive medication, where close monitoring of side-effects is important. However, there is widespread uncertainty relating to which of these potent drugs to use. A recent survey (TREAT)³ among paediatric dermatologists from eight European countries reported that ciclosporin was the drug of choice for both first-line and second-line use overall (43% and 33% of responders, respectively), while 17.2% chose methotrexate as second-line and 26.2% as third-line medication. Variations in practice likely stem from a paucity of evidence surrounding the use of systemic therapies for severe recalcitrant eczema in children. One case series of methotrexate in 25 children with refractory discoid eczema reported complete clearance in 16 patients and partial clearance in three, with no adverse events seen.⁴ There is certainly more evidence to support the use of ciclosporin to treat childhood eczema, but the only published randomized controlled trials (RCTs) to date were placebo controlled.^{5,6} There have been no RCTs comparing two active systemic therapies in children with severe eczema, and therefore this study by El-Khalawany *et al.*⁷ is the first of its kind.

Strengths of the research

This RCT is the only head-to-head comparison of methotrexate vs. ciclosporin in children with severe recalcitrant eczema. It was not industry sponsored and the investigators had no conflicts of interest, making biased interpretation less likely. Markers of good reporting in this study, as per the CONSORT guidelines,⁸ include: (i) clearly stated outcome measures, (ii) explicit descriptions of inclusion and exclusion criteria, (iii) use of a table displaying baseline characteristics of both groups, and (iv) detailed reporting of adverse effects.

Assessment of validity

Internal validity

Randomization

Participants were randomized in a 1 : 1 ratio using a computer program. At baseline, both treatment groups comprised 20 children and had similar demographic and clinical characteristics, implying a reasonable randomization process. This in turn should have served to minimize selection bias.

Comment

What is already known about this topic?

Eczema (synonymous with 'atopic dermatitis' and 'atopic eczema') is the most common chronic inflammatory skin condition, affecting approximately 20% of children in the U.K.¹ Its detrimental impact on quality of life is comparable with other chronic diseases of childhood such as diabetes and asthma, and it represents a significant and growing burden on

Blinding

Unfortunately, the authors gave no information regarding the method of blinding in this study. Due to the overtly differing administration regimens of methotrexate and ciclosporin (weekly vs. daily), it is likely that at least the participants were unblinded to their treatment allocation. However, in order to evaluate the risk of ascertainment bias, it would be important to clarify this and also whether the outcome assessors were blinded or unblinded.

Intention to treat

The authors did not comment on whether an intention-to-treat analysis was used, or whether any participants dropped out before the end of the trial. This information is crucial in order to evaluate risk of attrition and selection bias.

Power

No power calculation is shown in this report, and it is therefore unclear as to how the investigators arrived at 40 as the number of participants required to detect a difference between the two active treatments. There is also no mention of the minimum clinically important difference (MCID) in terms of SCORAD points, a value that would directly impact on any power calculation. A difference in the SCORAD of 8–9 units has been suggested as the MCID for trials using systemics in severe eczema.⁹ It is also worth noting that the 40 participants in this study are similar in number to the 42 adult patients with eczema included in a similar RCT of methotrexate vs. azathioprine, which was likely to be underpowered to show 'noninferiority'.^{10,11}

External validity

In this study, patients 'diagnosed with severe atopic dermatitis', who failed on topical therapy and who were unfit, uncooperative or poorly responsive to phototherapy, were recruited from outpatient dermatology clinics at four different university hospital centres. No further information is provided on whether specific criteria or validated eczema severity measures had been used to confirm a diagnosis of severe eczema. The mean age of participants was 11.6 ± 1.52 years, with a mean disease duration of 6.80 ± 1.83 years, representing a population with the majority of childhood affected by chronic eczema. Although these findings are not immediately generalizable to the paediatric population as a whole, external validity is likely to be good in the context of children with severe recalcitrant eczema.

The primary efficacy outcome in this study was the mean change in SCORAD measured at 12 weeks, and as Patel *et al.*¹² have commented in a recent critical appraisal of a similar RCT in adults, this is arguably too soon in the context of treating chronic refractory disease. If we suppose that some clinicians would persevere with an initial systemic therapy for a period

longer than 12 weeks, then longer treatment regimens and follow-up periods may have provided useful additional information.

Other issues

Although informative, the title of this study does not convey its RCT status as per the CONSORT guidelines, and there is no flow diagram explicitly depicting the passage of participants through the four stages of the trial (enrolment, intervention allocation, follow-up and analysis). The study does not appear to have been registered on a trial registry, despite the stated policy of the International Committee of Medical Journal Editors.¹³ The start and end dates of the trial are not given.

The authors specified a 2-week wash-out period for all topical or systemic treatments except emollients prior to commencing the study. As Patel *et al.*¹² have previously commented, this is relatively short and may have led to underestimation of treatment efficacy in patients previously on systemic therapies. Unfortunately, there is no mention of whether trial participants were naive to any systemic immunosuppressive therapy. It would also be important to know whether topical anti-inflammatory and emollient therapies were allowed alongside systemic immunosuppressants and, if so, whether their use was similar in both study arms.

Systemic drug doses in children are usually based on weight per kilogram, and it was arguably inappropriate to start study participants in group A on a fixed dose of methotrexate 7.5 mg weekly. Furthermore, it is likely that most children were undertreated, as this dose equates to a maximum body weight of 37.5 kg using even the lowest recommended dose of 0.2 mg kg^{-1} per week. Similarly, ciclosporin 2.5 mg kg^{-1} per day, as administered to the children in group B, is a low dose compared with the European standard dose of 3.5 mg kg^{-1} per week.³ This potential underdosing may account for the apparent similarity in speed of onset between methotrexate and ciclosporin, as shown in the report's figures. Dermatologists may find this puzzling, as methotrexate appears to take at least 2 months to bring about clinical improvement, whereas ciclosporin usually works within a month. In the context of the 3-month treatment duration chosen for this study, perhaps it would have been more appropriate to compare methotrexate with azathioprine, which appears to have a similar speed of action.

The authors utilized the SCORAD index as the sole measure of eczema severity. This comprises both objective and subjective elements and is well validated, but the use of more than one disease measure may have proved useful in supporting the primary results. Possible secondary outcome measures in such trials include Investigator Global Assessment, Patient Global Assessment, Eczema Area and Severity Index, and Patient-Oriented Eczema Measurement. Given that this is the first RCT to compare systemic therapies for eczema in the paediatric setting, the absence of specific patient- and carer-rated outcomes is also notable.

Overall assessment (including any potential application of the research to clinical practice)

This study suggests that short-term low doses of methotrexate and ciclosporin may be equally effective, safe and well-tolerated treatments for children with severe recalcitrant eczema. The study had a reasonable treatment period of 12 weeks, followed by an adequate follow-up period. The authors gave helpful information about how they administered low doses of the drugs, and provided full reports of any adverse effects encountered. Indeed, it is interesting that adverse effects were quite common even at these low doses, and this may have ramifications for clinical use. It is also worth noting that the potential for renal toxicity with ciclosporin makes it less suitable for long-term treatment, which is often required in this severe subgroup of patients with eczema. Methotrexate may therefore offer an appealing alternative to ciclosporin and also to azathioprine, which has been associated with safety concerns of its own, including increased risk of lymphoma,^{2,14} while methotrexate has a good safety profile based on long-term follow-up of paediatric rheumatology cohorts.

This study had a small sample size, is likely to have been underpowered, and could have been reported more thoroughly on several counts, including the important issues of blinding and intention-to-treat analysis. Indeed, it is difficult to provide an accurate evaluation of this RCT's quality in the absence of such information.

However, El-Khalawany et al. are to be congratulated for undertaking the first RCT to address the uncertainty surrounding the use of systemic eczema therapies in the paediatric population. Their comparison of methotrexate and ciclosporin in this setting will undoubtedly stimulate future research into the long-term efficacy and safety of immunosuppressant agents, hopefully utilizing larger numbers of patients and longer periods of treatment and follow-up.

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Conflicts of interest: None declared.

Methotrexate vs. ciclosporin in the treatment of severe atopic dermatitis in children: author response

Thank you very much for the critical appraisal of our study.^{1–3} We would like to thank the authors of the appraisal for the valuable comments and the acknowledgment of our study.

Most of the comments were previously discussed with reviewers of the *European Journal of Pediatrics*, including the design of the study, dose of drugs, duration of follow-up and statistical analysis. We would prefer not to discuss these again because the study was modified and corrected in response to the reviewers' comments and suggestions.

We hope all readers take the critical appraisal's points into consideration during the preparation of similar studies.