

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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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.

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Commentary: Methotrexate and ciclosporin in the treatment of severe eczema in children

Severe and persistent childhood atopic dermatitis (AD) has a dramatic impact on quality of life. If AD remains poorly controlled after appropriate and well-adhered-to topical regimens have been exhausted, including assessment of immediate and delayed allergies and infective aggravations (bacterial, viral and fungal pathogens),¹ what is the next option on the treatment menu? Narrowband phototherapy is often an attractive option. When other treatments have been exhausted, paediatric dermatologists not infrequently find themselves offering advice and choices to families considering systemic therapy. Clearly, any treatment offered must be both effective and safe, not just in the immediate term but, especially in a paediatric population, in the long term too. What evidential basis do we have to inform and guide parental and child choice?

The truth is that direct evidence is hard to find, as primary data from properly conducted clinical trials of systemic therapies in severe childhood AD are very few, and thus we often must extrapolate backwards from adult studies or from the use of these drugs in childhood for other indications. Neither situation is ideal: in the first instance due to the very different pharmacokinetic and dynamic considerations in children, and in the second for the obvious disease-specific variations in response to therapy. As a subspecialty, paediatric dermatology has not succeeded in exploring, in a robust and systematic way, the best options in this clinical scenario. In this setting any new evidence is very welcome and is worth examining

closely to see whether it can substantiate a change in clinical practice. Current therapeutic choices in this situation include ciclosporin, azathioprine and methotrexate. Ciclosporin is licensed for use in over 16 year olds and remains the systemic therapy of first choice in most of Europe.² Azathioprine has been widely used in the U.K., but recent reports of late side-effects with this drug have understandably given cause for concern on safety grounds;³ these include skin cancer, hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, albeit in other disease settings and often in conjunction with other immune-modifying drugs.

Recently, Schram et al.⁴ conducted a randomized controlled trial (RCT) comparing methotrexate with azathioprine in severe AD in adults. This work reignited interest in the possibilities of using methotrexate in AD. Given that methotrexate is such a well-established drug in dermatology, and is so familiar to dermatologists for other indications (especially psoriasis, for which it has been used since 1961), it is surprising that it never occurred to the dermatology community to study this agent systematically in AD. The study suggested that both methotrexate and azathioprine were effective and safe in the short term in AD, and that these effects appeared to be of similar magnitude. However, it was underpowered to make definitive efficacy comparisons between the drugs.

There is no direct comparative RCT evidence to guide a choice between any systemic therapies in childhood AD. El-Khalawany et al.⁵ report the first clinical trial in paediatric AD comparing low-dose ciclosporin vs. low-dose methotrexate. They chose low doses of each agent: ciclosporin was used at a dose of 2.5 mg kg⁻¹ per day, well in the lower therapeutic range of 2–5 mg kg⁻¹ per day, while methotrexate was kept at a fixed dose of 7.5 mg per week with no allowance for weight or variable absorption. As higher doses of each agent are routinely used in clinical practice, these choices limit the clinical translatability of their findings. Notwithstanding this consideration, the SCORing Atopic Dermatitis improvements in each treatment group are impressive. As ciclosporin is known to be effective in AD in children, the major novelty of this report is to show that methotrexate is also effective and safe, within the short trial period here, and at a low dose. However, the study would not fully meet the CONSORT guidelines demanded by the BJD and other journals. Tsakok and Flohr, in their critical appraisal,⁶ note the lack of intention-to-treat analysis as a study weakness. I found that the very similar treatment response curves between methotrexate and ciclosporin differ from my experience, where I usually expect methotrexate to take several weeks longer to reach maximum efficacy. I would also like to have seen longer-term follow-up, including after treatment cessation, as this is a key question for parents and a possible area where methotrexate could outperform ciclosporin, a drug with a high relapse rate after treatment.

Despite these issues, El-Khalawany et al. have done the specialty a favour by putting methotrexate on the menu for consideration in the setting of severe AD in childhood, and their work will stimulate larger, more definitive trials. In fact, in