

Putting papers into practice – BJD

Commentary:

Methotrexate and Ciclosporin in treatment of severe eczema in children

ORIGINAL ARTICLE: El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt.

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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 including bacterial, viral and fungal pathogens dealt with¹ what is the next option on the treatment menu? Narrow band 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 subspeciality paediatric dermatologists have not succeed 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 if it can substantiate a change in clinical practice. Current therapeutic choices in this situation include cyclosporine (CSA), azathioprine (AZA) and methotrexate (MTX). Cyclosporine is licenced 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 UK but recent reports of late effects with this drug including skin cancer, hepatosplenic T cell lymphoma and progressive multifocal leukoencephalopathy, albeit in other disease settings and often in conjunction with other immune modifying drugs, have understandably given cause for concern on safety grounds.³

Recently, Phyls Spuls and co-workers conducted a RCT comparing MTX with AZA in severe AD in adults.⁴ This work reignited interest in the possibilities of using MTX in AD. Given that MTX is such a well established drug in dermatology and so familiar to dermatologists for other indications most especially psoriasis where it had been used since 1961, it is surprising that it never occurred to the dermatology community to systematically study this agent in AD. The Spuls study suggested both MTX and AZA were effective and safe in the short term in AD and that these effects appeared to

be of similar magnitude but 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 atopic dermatitis comparing low dose ciclosporin vs low dose methotrexate. They chose low doses of each agent: CSA was used at a dose of 2.5 mg /Kg/day, well in the lower therapeutic range of 2-5 mg/Kg/day, while MTX was kept at a fixed dose of 7.5 mg per week with no allowance for weight or for 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 SCORAD improvements in each treatment group are impressive. As ciclosporin is known to be effective in AD in children, the major novelty to this report is to show that MTX is also effective and safe, within the short trial period here, and at low dose. The study would not meet fully the CONSORT guidelines demanded by the *BJD* and other journals. Tsakok and Flohr, in their critical appraisal, note the lack of an intention to treat analysis as a study weakness. I found the very similar treatment response curves between MTX and CSA to differ from my experience, where I usually expect MTX 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 MTX could outperform CSA, a drug with a high relapse rate after treatment. Despite these issues, El-Khalawany *et al* have done the speciality a favour by putting MTX 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 recent years I have increasingly used MTX as a systemic of first choice in severe AD due to the favourable short and longer term adverse effect profile and, in my view, lower chance of relapse after treatment cessation compared to CSA. In my experience MTX has performed well and with comparable efficacy to CSA and AZA, though the time to full clinical effect can be up 12 weeks and may require doses of 0.4 mg/Kg/week.

I hope this work will stimulate further comparative study of MTX and CSA, including longer term treatments and larger numbers of patients, and including long term follow up after treatment cessation. Further work on the mechanism of action of MTX in AD would also be valuable. In parallel to determining the relative safety and efficacy of these agents in childhood AD, work is needed to establish agreed protocols for initiating these agents

in childhood AD, including pre- and during-treatment safety monitoring and treatment duration guidelines.

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