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Response to a randomized trial of methotrexate vs. azathioprine for severe atopic eczema: a critical appraisal

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Patel and colleagues¹ have written a critical appraisal of our study² 'A randomized trial of methotrexate versus azathioprine for severe atopic eczema'. The authors have made a very thorough appraisal of our study with many educational aspects and relevant comments concerning the internal and external validity. Furthermore, we thank the authors for drawing attention to our study in a dermatology-specific journal. This will benefit patients with severe atopic eczema.

Hereby we would like to take the opportunity to present our comments on some of the statements.

Power

In our study, we have performed our power analysis in the absence of a formally calculated minimal clinically important difference (MCID) and we decided that an MCID of 8 points

on the SCORAD was appropriate to use. It can be argued that the MCID could have been smaller. In that case our sample size would have been inadequate to detect a difference. However, we have just performed a clinimetric study assessing the MCIDs of different outcome parameters including the SCORAD.³ Here we found that the MCID of the SCORAD was 8.7 points. It is known that MCIDs may vary by population and context and thus a single MCID may be insufficient for all study applications. Nevertheless, it is an indication that our decision to use an MCID of 8 points was appropriate.

Blinding

We fully agree with the comments made about the blinding. Additionally, we stress that for this investigator-initiated, non-sponsored study it would have been very expensive to blind the patients. In randomized controlled trials, patients, physicians, the randomization, the outcome assessment (efficacy and safety) and the statistician performing the analyses could be blinded. In our study we met three of these five possibilities.

Wash-out

Wash-out was indeed relatively short and might have made the found treatment effect smaller. We were aware of that fact when we designed the study. Our consideration was the well-being of our patients. Atopic eczema has a fluctuating course and 4 weeks without potent topical corticosteroids and/or systemic therapy in severely affected patients was considered unethical.

Rescue medication and other issues

We agree with the statement that allowing patients to start or continue topical steroids and receive rescue medication could have had an impact on the change in SCORAD. Nevertheless, the total amount of topical steroids was low and equal in both groups and rescue medication was only allowed in the first 8 weeks.

Patients were allowed to stop or switch between study medications at week 12. This might have had an effect on our results at week 24. Our primary outcome measure was the SCORAD at week 12 and thus an effect on primary outcome is not expected.

Conclusion

Given the recently reported MCID in SCORAD³ the raised concern of limited statistical power of our study can be ruled out. We agree with the authors (as we stated in the discussion section of our initial article) that future studies should focus on children, long-term efficacy and safety and comparative studies.

Currently, we have initiated a 5-year follow-up study for our study patients to obtain long-term data.

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Conflicts of interest

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Commentary: are methotrexate and azathioprine really equivalent for treating severe atopic eczema?

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I agree with Patel and colleagues¹ that there is a clear need to evaluate long-term systemic therapies for people with severe atopic eczema, and Schram and colleagues² are to be congratulated for undertaking an independent randomized controlled trial of two active therapies: methotrexate and azathioprine. Patel et al. have discussed some factors that might have affected internal validity of the study which are openly discussed by the report authors – an attitude which is to be commended.^{1–3} I agree with the authors that complete blinding would have been very difficult, expensive

and possibly dangerous for drugs that are given in such a different way, i.e. methotrexate is given weekly with folic acid and azathioprine is given daily.³ So the emphasis in such a study is to include objective outcomes in order to mitigate the risk of detection bias. With this in mind, it should be noted that the stated primary outcome (SCORAD) contains two subjective elements. Thankfully, other outcome measures such as Investigator Global Assessment (IGA), which can be completely objective if based on skin examination alone, were used. Making sure that the study protocol was registered prospectively in a publicly accessible website as required for all *British Journal of Dermatology* trials was also good practice,⁴ and the study was quite well reported with useful data such as standard deviations and a participant flow diagram.

As someone with an interest in atopic eczema, the question I ask myself having read this study is whether I believe the authors' conclusions that 'methotrexate and azathioprine can be considered equally effective for the treatment of atopic eczema in adults'.² I am not so sure.

Let's go back to the main hypothesis of this study – was it set up to show that one of the treatments was better than the other, i.e. a superiority study, or was it set up to show that they were similar to the other with reference to a pre-determined margin of equivalence, i.e. an equivalence study?⁵ No clear statement of the study hypothesis is provided in the report, although a statement in the analysis section, 'we deemed it appropriate to use an 8-point difference in SCORAD scores between the groups as the non-equivalence limit' implies that maybe the study was designed with demonstrating equivalence in mind. Thankfully, the trial registration document helps us out because it contains a clear study hypothesis statement: 'we hypothesize that methotrexate and azathioprine will be equally effective for the treatment of severe atopic dermatitis' (<http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1916>, last accessed 21 December 2011). The key statistic therefore in determining whether equivalence was achieved is the 95% confidence interval (CI) around the difference in change of SCORAD between the two treatments, and whether such an interval falls within the 8 points boundary. I could not find this key 95% CI in the abstract or body of the paper – in fact, I could not find any 95% CIs at all, despite the fact that the CONSORT statement for good clinical trial reporting encourages their use.⁶ Luckily, the authors have provided us with all the necessary data in Table 2 of their report for me to estimate the 95% CIs for you. The mean reduction in SCORAD for methotrexate was 22.7 points,^a and for azathioprine it was 22.2 points, a difference of 0.5 points in favour of methotrexate, with 95% CI ranging from –7.7 to 8.7, i.e. outside the prespeci-

^aThe value of 22.2 for mean reduction in SCORAD for azathioprine in Table 2 of the report differs from the corresponding value for the figures given in the text for azathioprine, i.e. 58.0–36.3 = 21.7. I have used the numbers given in Table 2.