

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.

fied equivalence margin of 8 points. Let's not be pedantic here, as one could argue that 8·7 is much the same as 8·0, and is curiously identical to the value of 8·7 points defined as a minimum clinically important difference in a subsequent study performed by the same group.⁷

I don't know about you, but I find it difficult to decide whether an 8-point difference in change in SCORAD really does mean that the two treatments are about the same, so I have to turn to the other outcomes that are easier to interpret clinically. The report stated that the primary outcomes included mean relative and absolute changes in SCORAD at 12 weeks, but on reading the trial registration document I was surprised to find the following additional three primary outcomes lurking there: (i) mean change of IGA between the two groups at 12 weeks; (ii) comparison of the proportion of subjects with a SCORAD reduction of 50% or more; and (iii) the proportion of subjects with an IGA of clear/almost clear/mild at 12 weeks. None of these additional primary outcomes is called a primary outcome in the report, and several additional secondary outcomes have appeared in the report that were not present in the trial registration document.

Thankfully, complete data on the original planned primary outcomes are included in Table 2 of the report, so let me give you the full analysis of these important outcomes plus 95% CIs to see if it helps you decide whether the treatments were equivalent. The mean reduction in IGA was 1·8 for methotrexate and 1·4 for azathioprine, a difference of 0·4 in favour of azathioprine (95% CI -0·11 to 0·91). Now that sounds quite a large possible range of plausible differences given that an IGA of 1·0 represents a change in category of clear, almost clear, mild, moderate, severe or very severe. With regard to the proportion of participants with a SCORAD reduction of 50% or more, 40·0% in the methotrexate group achieved this threshold compared with 45·4% in the azathioprine group, a difference of 5·4% in favour of azathioprine (95% CI -2·4 to 35·4%). Those CIs are really starting to look quite wide now. Finally, for the proportion of participants with an IGA of clear/almost clear/mild at 12 weeks, these correspond to 75·0% for methotrexate and 68·2% for azathioprine, a difference of 6·8% favouring methotrexate (95% CI -20·4 to 34·0%). That means that the results are compatible with methotrexate being up to 34% better than azathioprine or up to 20% worse – not a strong basis for claiming therapeutic equivalence.

So having looked at a few outcomes that I can relate better to in clinical practice (and which were prespecified as primary outcomes in the trial registration plan), I am unconvinced that this study has demonstrated therapeutic equivalence between methotrexate and azathioprine. Much larger studies than 42 patients are probably needed to demonstrate such equivalence more convincingly.⁸

Another slight surprise in the study for me was that the mean SCORAD response curves in Figure 2 were almost

identical for both treatments. I am not disputing the data as they show what was found in this study. My clinical experience is that azathioprine has a slower onset of action (around 2 months) to reach maximal effect whereas the effects of methotrexate are noticeable within around 4 weeks. Perhaps my experience is based on an incorrect notion, and it is important that future studies include such speed of response data.

This study is an important contribution to the literature on systemic therapy for atopic eczema, which has historically been lacking.⁹ The study illustrates the usefulness of prospective registration of clinical trial protocols on publicly accessible trial registers and the importance of presenting all the data so that readers can explore all important outcomes. I use both drugs for treating severe atopic eczema, and the lack of short-term serious adverse events in the trial has given me a little more confidence to continue to use either. I am still not sure which one is better or whether they are about the same, so hopefully this study will stimulate larger similar studies in adults and children and that the data will continue to have a second life by contributing to systematic reviews that are able to combine the data with other studies using common outcomes such as those being developed by the HOME initiative.¹⁰

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