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Looking beyond placebo-controlled trials

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Response title:

Looking beyond placebo-controlled trials

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To The Editor

We thank Siegfried et al. (Siegfried *et al.*, 2017) for their thoughtful response to our recent editorial (Flohr and Weidinger, 2016) in the *JID*. Like our US colleagues, we strongly support more clinical trials testing new therapies for children with atopic dermatitis (AD). It is heartening to hear that the authors, together with others from the US Pediatric Research Alliance, the US National Eczema Association and the International Eczema Council are preparing a guidance document for industry on the conduct of pediatric AD trials. We also sympathize with the obstacles faced by US investigators, as US regulators insist on placebo- and vehicle-controlled trials for drug approval and their emphasis on FDA-approved drugs for use in later phase active-comparator trials.

Nevertheless, Siegfried et al. acknowledge that active-comparator clinical trials are possible in a US environment, albeit with a limited number of therapeutic agents due to the dearth of FDA-licensed drugs for topical (corticosteroids, calcineurin inhibitors, and phosphodiesterase inhibitors) and systemic AD therapy (oral corticosteroids). Interestingly, our recent collaborative project with the US Pediatric Research Alliance has shown that US and Canadian clinicians do not follow FDA licensing (oral corticosteroids) when it comes to treating children with severe AD and most commonly use cyclosporine (45.2%), methotrexate (29.6%), and mycophenolate mofetil (13.0%) as first line systemic agents, rather than oral corticosteroids (Totri *et al.*, 2017), which is in line with recommendations of guidelines for the treatment of pediatric and adult atopic dermatitis published by several different medical societies internationally (Weidinger and Novak, 2016). In this context we welcome the authors' statement that 'during phase 4, a study using an off-label, standard-of-care treatment, like methotrexate, would be feasible and tremendously valuable for clinicians.' This would not only be valuable for dermatologists but also patients alike, as they would not be denied active therapy.

Drug efficacy is not everything, however, and there clearly are differences between European and US regulatory authorities and health service provision that additionally come into play. For instance, cyclosporine, not oral corticosteroids, is the only licensed drug for the treatment of recalcitrant AD.

In addition, active-comparator clinical trials are now standard in Europe, certainly beyond the initial early phase trials, after drug efficacy and short-term safety have been proven. Although not identical in their set up, all European countries have a basic provision of health care for their citizens funded through taxation, and health care resources are therefore limited, making health technology assessments an essential part of the decision whether a treatment is provided by a health service and covered by health insurance companies. For instance, the UK National Institute for Clinical Excellence (NICE) requires a comprehensive health economic evaluation that hinges on the cost of a drug in relation to its improvement in health-related quality of life (cost per QALY) to inform their treatment recommendations and guideline development (NICE, 2014).

It is true that active comparator trials need to be larger than placebo- or vehicle-controlled ones to show superiority over the established active treatment. This may well make drug companies less likely to invest, as Siegfried et al. say, especially since such RCTs are not only more costly but also risk to show small if any additional benefit from the new and usually more expensive agent. However, comparative clinical trials are important to supplement the basic definition of efficacy from placebo studies, and it is essential for clinicians to have such information to inform their decision-making and indeed for a health service to decide whether reimbursement of a new treatment is worth tax payers' money.

Like Siegfried et al. we feel that systematic reviews of placebo-controlled trials are compromised by methodological diversity and differences in the study populations, making direct comparisons between therapies difficult. In our view, this is another good argument for active-comparator trials. It is important to keep in mind, however, that RCTs cannot answer all important questions. Due to very stringent inclusion and exclusion criteria the patients they recruit are often not representative of the patients we encounter in daily clinical practice. They are relatively short and rarely follow patients up post treatment cessation and thus do not provide data on long-term disease control and drug safety. This requires observational cohorts of 'real world' AD patients. With this in mind, the international TREAT (TREATment of ATopic dermatitis) Registry Taskforce has been set up to

harmonize data collection in national AD treatment registries across country and continental borders, and we look forward to working with our North American colleagues on this important project (<http://www.comet-initiative.org/studies/details/825>).

ACCEPTED MANUSCRIPT

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