TO THE EDITOR

We thank Siegfried and colleagues (2017) for their thoughtful reflections on our article, and we note their significant industry conflicts (Feng et al., 2016). Although their comments mainly relate to commercial studies and how they plan to lobby the US Food and Drug Administration in relation to their preference for streamlining atopic dermatitis (AD) trials, they make some valuable points in relation to choice of vehicle or active comparator, which was the main thrust of our article (Wilkes et al., 2016).

Their point that not all vehicles and emollients are the same is well taken, as is the notion that such vehicles might have some active mild anti-inflammatory properties in their own right (van Zuuren et al., 2017). Such activity might account for some of the benefits frequently observed in study participants receiving vehicle only, along with other reasons such as increased adherence to standard care, regression to the mean, expectation bias, and other nonspecific effects associated with trial participation. We also agree that there is a clear need for vehicle controlled studies in the initial development of a new topical to demonstrate efficacy, especially to avoid the problem of an underpowered study of one active compound against another that equates finding no evidence of a difference as evidence of equivalence—which is clearly wrong (Williams and Seed, 1993).

For topical treatments, we still maintain that once efficacy has been shown through two or three studies comparing the active product to a vehicle (or comparable emollient), active comparator studies should be the norm thereafter so that doctors and patients across the world can judge how the new treatment compares against the standard treatments that they currently use. It is our hope that all new topical treatments, such as crisaborole, which has shown a clear but small benefit compared with vehicle in two very large pivotal studies required for licensing purposes (Paller et al., 2016), will now rapidly progress to studies using active comparators and that the days of conducting 25 vehicle/emollient randomized controlled trials (RCTs) for new AD products, as was the case with pimecrolimus, will be a thing of the past. We suggest that the standard comparator for RCTs of topical products targeting mild to moderate AD should be a mild or moderate topical corticosteroid (TCS) such as hydrocortisone or clobetasone. Such a real-world study was done for the largest and most informative long-term study of topical pimecrolimus (Sigurgeirsson et al., 2015). New topicals targeting moderate to severe AD should be tested against potent TCSs such as fluticasone or mometasone used once daily.

We disagree with the authors’ suggestion that TCSs should be considered as standard comparators only for treatment of intermittent flares and that topical calcineurin inhibitors should be the standard comparator for long-term maintenance treatment. Systematic review evidence suggests that TCSs are very good, if not better, for long-term control when used as proactive therapy for two consecutive days per week when compared with topical calcineurin inhibitors (Schmitt et al., 2011), and they are much cheaper and with very few safety problems when used as recommended.

To minimize a confusing array of “me-too” products, we would also suggest that new topical treatments need to be better than existing safe and effective topical treatments and that studies testing new topicals should be powered for study superiority. A noninferiority or equivalence study design would need to make the case for a strong tradeoff between similar effectiveness and lower cost, better patient tolerance, or fewer adverse effects to be justified. If skin thinning is the main rationale for introducing an alternative to TCSs for example, then a clinical trial of the alternative treatment should test that rationale by including an active TCS comparator and measuring clinically significant skin thinning in a blinded assessment in the treatment groups, provided that the TCSs are used in a way that mimics responsible routine clinical care.

After many vehicle-controlled studies of pimecrolimus, that was exactly what the PETITE study did (Sigurgeirsson et al., 2015): compare long-term topical pimecrolimus with long-term use of mild to moderate TCSs, only to find that there was no problem with clinically significant skin thinning with TCSs used in this way. Such a key result did not feature in the original publication (Sigurgeirsson et al., 2015) but eventually emerged after three requests for such data (Sigurgeirsson and Luger, 2015).

We also suggest that the concept of “topical steroid sparing” is not a good outcome for trials of AD—why would one want to spare an effective and safe treatment if used appropriately? One does not hear of asthma trials that try to “spare” appropriate anti-inflammatory inhaled corticosteroids as if it is a good thing. Unfortunately, there is considerable phobia regarding the safety of TCSs (Aubert-Wastiaux et al., 2011) that is not borne out in clinical practice and evidence summaries, and the notion that steroids are bad is a promotional gift to those wishing to introduce and promote alternative products that may be less effective when tested against topical corticosteroids.

With regard to the choice of active comparators for oral or systemic treatments, we agree wholeheartedly with the...
authors that oral prednisolone is not an appropriate comparator. The only substantial RCT of oral prednisolone had to be stopped because of severe rebound flares when treatment was reduced (Schmitt et al., 2010). However, other systemic treatments such as ciclosporin (which is licensed in several countries) or oral methotrexate or azathioprine are perfectly adequate standard comparators for new systemic products (Roekevisch et al., 2014). Regulatory problems have not stopped other independent researchers from evaluating such comparisons, such as the ongoing TREAT study that is comparing ciclosporin against methotrexate for severe AD in the UK (TREAT, n.d.).

We agree with the authors that more RCTs in AD should be conducted in children and would add that more need to be conducted in the community (Nankervis et al., 2016), where most AD care occurs across the world.

CONFLICT OF INTEREST

The authors state no conflict of interest.

Sally R. Wilkes1, Helen Nankervis1, Elsa Tavernier2, Annabel Maruani3 and Hywel C. Williams1,∗

1Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK;

2CHRU Tours, Clinical Investigation Center–INSERM 1415, France; and 3University Francois Rabelais Tours-EA 4275, Department of Dermatology, France.

∗Corresponding author e-mail: hywel.williams@nottingham.ac.uk

REFERENCES


1366 Journal of Investigative Dermatology (2017), Volume 137

Looking beyond Placebo-Controlled Trials


TO THE EDITOR

We thank Siegfried et al. (2017) for their thoughtful response to our recent editorial (Flohr and Weidinger, 2016). 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, because US regulators insist on placebo- and vehicle-controlled trials for drug approval and emphasize drugs approved by the US Food and Drug Administration (FDA) for use in later-phase active-comparator trials.

Nevertheless, Siegfried et al. (2017) acknowledge that active-comparator clinical trials are possible in a US environment, albeit with a limited number of therapeutic agents because of the dearth of FDA-licensed drugs for topical (corticosteroids, calcineurin inhibitors, and phosphodiesterase inhibitors) and systemic AD therapy (oral corticosteroids). 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 and guidelines for the treatment of pediatric and adult AD 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