



Optimizing Clinical Trials for Atopic Dermatitis in Children

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TO THE EDITOR

We read with interest and appreciate the recent manuscript by Wilkes et al. (2016) that broadly assesses the body of randomized controlled clinical trials that exist for atopic dermatitis (AD). We agree with many of the AD research issues raised in the accompanying editorial by Flohr and Weidinger (2016). The growing AD treatment pipeline brings a sense of urgency to defining optimal protocol design for AD clinical trials. Critical parameters include the study subject population, endpoints, and use of comparators.

Although Wilkes et al. (2016) documented that a substantial minority of trials involving topical calcineurin inhibitors used inactive controls, their analysis did not distinguish between the use of vehicle versus a different emollient as the inactive control. In some cases, it may not be feasible to formulate a vehicle with exactly the same excipients, omitting only the active ingredient. Although there is no published guidance or regulations from the US Food and Drug Administration (FDA) governing this matter, the E10 Conference on Harmonisation (US Food and Drug Administration, 2001) recognizes that placebo vehicles may not be completely inactive. The degree of vehicle/emollient response can significantly affect between-group comparative responses. In most vehicle/emollient-controlled trials, AD improves to a variable degree in subjects in the inactive comparator arm, decreasing the between-treatment difference (Paller et al., 2016). Conversely, vehicle group worsening is an uncommon reason for enhanced between-treatment efficacy (Abramovits and Boguniewicz, 2006).

Flohr and Weidinger's (2016) commentary emphasized that placebo-controlled trials create research waste. Currently, the FDA requires unspecified placebo- or vehicle-controlled trials for drug registry studies, whereas use of an active comparator is the standard format for clinical trials in Europe. Placebo- or vehicle-controlled trials are invaluable before phase 3 or 4 studies for establishing superior efficacy and evaluating short-term safety and tolerability. In addition, only a placebo control can minimize the potential for "bio-creep," a phenomenon that may occur when a new treatment is misinterpreted as effective after serial comparative clinical trials have shown increasingly smaller, but noninferior, results (Everson-Stewart and Emerson, 2010). However, placebo- and vehicle-controlled trials deny some patients access to active therapy, raising ethical issues and taxing recruitment, especially for more severely affected patients (e.g., for systemic agents) and studies involving children. And although there are fewer reasons to include a placebo arm after early studies have suggested efficacy and the adequate safety needed for further testing, there are challenges to performing active comparator trials. The most significant is determining a non-inferiority margin, which is possible only after efficacy of the active comparator has been well established.

Active comparator clinical trials are possible for topical agents in AD because several drugs are FDA-approved to treat this disease in adults and children: topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs) such as pimecrolimus and tacrolimus, and a new topical phosphodiesterase-4 inhibitor, approved

December 14, 2016 (US Food and Drug Administration, 2016a). The ideal choice of an active comparator for AD trials, however, is dependent on the study hypothesis. For example, TCSs are generally considered more effective for intermittent treatment of flares, whereas TCIs are most often recommended for long-term maintenance therapy (Schneider et al., 2013; Sidbury et al., 2014). Therefore, a direct comparison between TCIs and TCSs is less meaningful than comparing a TCI with another steroid-sparing maintenance treatment, such as a phosphodiesterase-4 inhibitor.

Ironically, enteral/parenteral corticosteroids remain the only systemic medication with FDA approval for severe AD, given many potential adverse effects, high risk of rebound after discontinuation, and published guidelines of care that recommend against their use (Schneider et al., 2013; Sidbury et al., 2014). Systemic corticosteroids are clearly not an appropriate comparator for the growing number of trials of systemic AD drugs. Because there are no other FDA-approved systemic agents to treat moderate to severe AD, active comparator trials may not be feasible for several reasons: medicolegal risk to sponsors and investigators associated with use of an off-label drug; study design considerations, for example, prior efficacy data that are required to adequately power a study; selection of an appropriate comparator with a similar safety-efficacy profile; and lack of consistent guidance among regulatory agencies. After the FDA approves the first safe and effective systemic agent for long-term treatment, this can serve as an active comparator in phase 2 and 3 trials, but it is likely that larger and potentially longer clinical trials will be required to observe smaller between-treatment differences. In some cases, the costs associated with establishing superiority against an active comparator (Blauvelt et al., 2017) may not

Abbreviations: AD, atopic dermatitis; FDA, US Food and Drug Administration; GDI, guidance document for industry; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

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ultimately yield a sponsor's return on investment, because price is often the driving factor for payors making formulary decisions. During phase 4, a study using an off-label, standard-of-care treatment, like methotrexate, would be feasible and tremendously valuable for clinicians.

In the absence of head-to-head comparative effectiveness trials, systematic reviews have been used to compare drug efficacy across AD trials (Roekevisch et al., 2014). Conclusions drawn from these reviews are compromised by variations in protocol design, inconsistent study endpoints, and differences in study subject populations. In many studies, particularly those investigating systemic medications, the disproportionate focus on adults and exclusion of children is particularly problematic, because children are more often affected by AD and may respond differently to treatment. FDA guidance has been published to inform pediatric drug development in general (US Food and Drug Administration, 2000, 2016b), but there are no specific recommendations for AD.

The Pediatric Dermatology Research Alliance, the National Eczema Association, and the International Eczema Council are supporting generation of a guidance document for industry (GDI), "Developing New Therapeutic Agents for Atopic Dermatitis in Pediatric Patients (0 to 18 years)." A panel of 33 experts, including clinicians, investigators from academics and industry, and patient representatives, are participating in the process. This draft GDI provides recommendations related to conducting pediatric AD clinical trials, including the use of placebo versus active comparator use. The draft GDI will shortly be submitted to the FDA Dermatology and Dental Products Division for review, with the goal of approval and ultimate distribution. During the next several years, clinical trials will define the effectiveness and safety of several new drugs for AD, the most common chronic skin disease in children (National Institute of Arthritis and Musculoskeletal Skin Diseases, 2016). The time is right to standardize and streamline clinical trials for AD in children.

CONFLICT OF INTEREST

Elaine Siegfried has received consulting fees and/or honoraria from Eli Lilly, GSK-Stiefel, Novartis, and Pfizer/Anacor. She served as an investigator for Pfizer/Anacor conducting atopic dermatitis clinical trials, and GSK-Stiefel as a Data Safety Monitoring Board member.

Jennifer Jaworski is a full-time employee of Prescott Medical Communications Group (Chicago, IL), which received financial compensation from Pediatric Dermatology Research Alliance, the National Eczema Association, and the International Eczema Council, in part, to support this work.

Lawrence Eichenfield has received consulting fees and/or honoraria from Eli Lilly, Genentech, GSK-Stiefel, Pfizer/Anacor, Medimetriks, Otsuka, Roivant, Sanofi/Regeneron, Valeant, and Vitae.

Adelaide Hebert has received speaking fees and/or honoraria from Anacor, Pfizer, Galderma, GSK, Roivant, and Menarini. She has served as an investigator for Galderma, Anacor, GSK, Celgene, Astellas/Leo, and Merz; all payments made directly to the University of Texas—Houston Medical School. She also serves as a member of data safety monitoring boards for Sanofi/Regeneron and GSK.

Amy Paller has received consulting fees from Eli Lilly, GSK-Stiefel, Novartis, Pfizer/Anacor, Puricare, Roivant, Sanofi/Regeneron, Valeant, Vitae, and Ziaco. She has served as an investigator in conducting atopic dermatitis clinical trials for Pfizer/Anacor and Astellas/Leo.

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