

A 5-year randomized trial on the safety and efficacy of pimecrolimus in atopic dermatitis: a critical appraisal – comment

Since the licensing of topical pimecrolimus over a decade ago, has the introduction of this 'steroid-free' therapy led to improvements in the treatment of children with atopic dermatitis (AD; syn. atopic eczema), particularly in the community where the majority of patients with mild-to-moderate disease are managed? How has research and clinical experience over the last decade clarified prescribing guidelines for pimecrolimus (PIM), particularly on body sites considered more susceptible to steroid side-effects such as the face and eyelids? Can PIM offer a clinical and cost-effective prescribing advantage, either in terms of avoiding irreversible steroid side-effects, or by reducing flare-ups and disease duration?

Clinical experience among many dermatologists suggests that undertreatment of childhood eczema in the community remains a common problem. Many primary care physicians remain reluctant to prescribe PIM owing to its cost and 'second-line' therapy status, yet continue to underprescribe topical steroids owing to steroid phobia. Undertreated eczema potentially increases the risk of further percutaneous aeroallergen sensitization and disease prolongation due to chronic skin barrier disruption and increased skin permeability, resulting in a vicious cycle of inflammation, sensitization and scratching. The effectiveness of topical calcineurin inhibitors (TCIs) has already been clearly demonstrated in clinical trials, but given their additional cost vs. topical steroids, this is not the primary issue that needs addressing to guide prescribers. If dermatologists are truly to improve the management of AD in infants and children in our communities and provide clear guidance on when to use PIM, it is the safety of long-term topical steroid therapy that needs clarifying.

PIM is currently recommended as second-line treatment for atopic eczema, particularly if the maximum strength and potency of topical corticosteroid that is appropriate for the patient's age and the area being treated has failed to control the AD, or where there is serious risk of important side-effects from further use of topical corticosteroids, particularly permanent damage to the skin.^{1–3} However, interpretation of this guidance varies widely between dermatologists, primary care physicians and pharmacists, as there is a stark lack of quantitative research data on long-term topical steroid safety to guide prescribers, particularly for facial and eyelid eczema in children. Can a mild topical steroid be safely used 2–3 times a week for 5 years or longer on the eyelids of a child without causing skin atrophy or ocular side-effects such as glaucoma or cataracts? Can a moderate-potency topical steroid be used for 3–5-day bursts regularly on a child's face for several years without causing skin atrophy or telangiectasia? Should TCI therapy be introduced in all children requiring mild or moderate topical steroids on the face more than twice weekly for long-term control, or is this frequency of topical steroid therapy safe? Could long-term use of topical steroids on the face

prolong disease progression due to subclinical skin thinning, allowing allergens or irritants to penetrate the skin more easily? Over 50 years of topical steroid prescribing has provided dermatologists with a wealth of steroid safety experience, but quantitative answers to these common questions affecting everyday prescribing decisions in general practice are still not available in the medical literature.^{4,5}

Unfortunately, despite a study duration of 5 years, the PETITE trial has been unable to clarify some of these important questions around optimum long-term AD therapy, as highlighted in the comprehensive accompanying critical appraisal. The PETITE study boldly claims to support the use of PIM as a first-line treatment of mild-to-moderate atopic eczema in infants and children, yet, surprisingly, the authors primarily base these recommendations on patient compliance issues due to 'steroid phobia', rather than demonstrating any new evidence for an efficacy or safety benefit over topical steroids. Despite highlighting the issue of steroid phobia, even the authors demonstrate lack of clarity around the true risks of steroid side-effects, stating in their response that they chose not to measure skin atrophy, as they felt it was *probably* not of major importance because there was only intermittent use of low- and medium-potency topical steroids throughout the study. Indeed, the overall mean use of topical steroids of only 178 days across the 5-year study period was very low (reflecting the rapid and sustained improvement in both groups at 3 weeks), but, nevertheless, by capturing both short- and long-term quantitative side-effect data, such as ocular assessments or skin ultrasound measurements, the study could have constructively addressed steroid phobia and clarified prescribing guidelines. Data on aeroallergen sensitization during and beyond the study period (after adjusting for disease control) would also be helpful in detecting any potential advantage for PIM on skin barrier function between flare-ups. While it is reassuring that the study showed no adverse effects of PIM or topical steroids on systemic immunity or response to vaccination in 3–12-month-old children (below the standard license age of 2 years), this reassurance is unlikely to increase appropriate prescribing of either PIM or topical steroids, when skin atrophy has not been addressed, and when the guidance for both preparations is so closely entwined.

Over a decade on from the licensing of TCI therapy, and over half a century on from the introduction of topical steroids for treating skin disease, many children in the community are still living with undertreated distressing AD, owing to confusion, conflicting messages and uncertainty around prescribing. Current national guidelines clearly state that anxiety around steroid use should not be an indication for TCI therapy, but that this anxiety should be addressed through effective patient information and education. However, topical steroid phobia has shown little signs of changing over the last

decade,⁶ and without evidence-based quantitative clarification on safe steroid prescribing, it remains difficult to convince many general practitioners to initiate or maintain ongoing prescriptions for either topical steroids or TCIs. Long-term studies in infants and children using topical steroids from infancy to adolescence or beyond are needed, using standardized noninvasive methods, such as ultrasound, to assess changes in whole skin and epidermal thickness (with adjustment for inflammatory skin thickening), as well as reversibility and ocular side-effects. Such studies are difficult to conduct but are absolutely necessary if topical steroid phobia is to be conquered in primary care.

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