

Editorial

Proactive therapy of atopic dermatitis – an emerging concept

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Atopic dermatitis (AD) is a chronic and highly pruritic skin disease with a broad spectrum of clinical manifestations. Atopic dermatitis has clearly increased by two- to threefold (prevalence of 15–30% in children and 2–10% in adults) during the past three decades in industrialized countries. As it is one of the most common of the skin diseases in developed countries, it has an increasing socio-economical impact. The direct cost is estimated almost 1 billion dollar in the United States alone (1). Pruritus, sleep loss, dietary restrictions and psychosocial affectations significantly lower the quality of life of AD patients (2).

The common long-term treatment concept for AD is based on daily application of emollients with or without antibacterial ingredients accompanied with symptomatic anti-inflammatory therapy consisting of topical glucocorticosteroids (TCS) or topical calcineurin inhibitors (TCI) on an 'as needed' basis (3, 4). This 'reactive' treatment approach is well established, widely accepted and the legal basis for all licensed TCS and TCI. Experienced physicians tailor this approach to every patient by choosing the optimal emollient and anti-inflammatory compounds eventually combined with UV-light, antihistamines and other treatment options.

Recently, an alternative treatment approach has been evaluated in clinical trials. This 'proactive' approach starts with an intensive topical anti-inflammatory therapy until all lesions have mostly cleared, followed by long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin together with daily application of emollients to unaffected areas.

On the one hand, identification of the most suitable treatment approach for AD as such calls for general evidence from basic science and immunobiology. On the other hand, clinical efficacy and safety studies, quality of

life assessments and pharmaco-economic data can only be produced by comparing specific, well-defined treatment strategies in clinical trials. As a long-term clinical trial comparing the proactive and reactive approach has been published in a recent issue of *Allergy* (5), this editorial covers general evidence from basic science and immunobiology as well as recent trial data supporting long-term proactive treatment strategies.

Defects of epidermal barrier function in AD lesions are mirrored by less pronounced, but clearly detectable similar defects in nonlesional AD skin, as recently reviewed by Proksch et al. (6). This barrier dysfunction results in an increased outside-in permeability of the stratum corneum for allergens in AD skin (7), corresponding to an increased inside-out permeability that may be assessed by measuring the transepidermal water loss in both lesional and nonlesional AD skin (8). The barrier dysfunction of nonlesional skin in close proximity to AD lesions is more pronounced than in regions distant from the florid lesions (9).

The increased permeability of nonlesional AD skin for large protein allergens is an important factor for the atopy patch test (10). Thus, protein allergens dissolved in petrolatum penetrate the epidermal barrier and elicit an eczematous skin reaction to the respective proteins (11).

Atopic dermatitis skin has been investigated by profilometric examination, showing intermediate smoothness levels for nonlesional AD skin, which are below normal skin but better than lesional AD (12). An analysis of the epidermal lipids essential for skin barrier function showed lower results for extractable long-chain fatty acids not just in lesional AD skin (75%) but also in nonlesional AD skin (60%) (13). Finally, several loss of function mutations of the Filaggrin gene have recently been detected in high association with AD (14, 15), leading to a barrier

defect and reflecting the clinical association of ichthyosis vulgaris to AD well known to clinicians for many years (16). This constitutive component of the barrier defect adds to the recently described, inflammation-induced component of the barrier defect (17) and will not go away even if the eczema is adequately treated.

The histopathology of nonlesional AD skin revealed features of mild disease with a low-grade inflammatory infiltrate, swelling of the endothelial cells, and thickening of the basement membrane zone (18).

Immunohistology showed that epidermal Langerhans cells are carrying IgE via the high-affinity IgE-receptor in lesional as well as in nonlesional skin of AD, but not in normal skin from nonatopic individuals (19–22). Quantitative flow cytometry demonstrated that Langerhans cells express significantly more high-affinity IgE-receptors on the cell surface in nonlesional AD skin than in normal human skin (23).

In conclusion, there is overwhelming evidence that normal-looking, nonlesional AD skin is not 'normal' at all, but is characterized by a clinically meaningful barrier function defect and a sub-clinical eczematous skin reaction.

The key parameters of clinical efficacy and safety, together with quality of life assessments and pharmacoeconomic data comprise the information needed for objectively appreciating the value of a proactive or reactive regimen. Only a few clinical trials have addressed all of these aspects in AD, but there is enough data to draw some conclusions:

In 2002, Hanifin et al. (24) published a randomized, double-blinded, 20-week clinical trial comparing the proactive application of either 0.05% fluticasone cream or placebo cream in 348 AD patients. The study cream was applied four times weekly for 4 weeks, followed by a twice-weekly application for 16 weeks. Patients proactively receiving 0.05% fluticasone cream were 7.7 times less likely to have an AD relapse than those receiving placebo. No skin thinning or atrophy was reported (24).

In 2003, Berth-Jones et al. (25) published a 16-week randomized, double-blinded clinical trial comparing the twice-weekly proactive application of either 0.05% fluticasone cream vs placebo cream or 0.005% fluticasone ointment vs the respective ointment placebo, recording among other parameters the principal outcome value 'time to first relapse'. The proactive regimen started after an initial high-intensity open-label treatment phase with once or twice-daily topical fluticasone. The proactive approach showed a highly significant advantage over the reactive approach, with a median time to relapse from 6 weeks for emollient alone vs > 16 weeks for both active preparations. The patients who applied the active cream were 5.8 times less likely and patients applying the active ointment were 1.9 times less likely to have a relapse than patients applying emollient alone (25). The different efficacy levels can easily be explained by (i) the higher

efficacy of ointment emollients as compared to cream emollients and (ii) the 10-fold higher concentration of fluticasone in the cream as compared to the emollient. The authors noted that the proactive regimen may paradoxically be steroid-sparing – an assumption not covered by the data provided in the publication but a reasonable assumption nonetheless.

Another study performed with methyl-prednisolone aceponate (MPA) against its placebo according to a similar protocol has shown that the probability of remaining free from relapse after 16 weeks was 87.1% in the MPA group compared to 65.8% for emollient. Methyl-prednisolone aceponate was also superior to emollient in terms of relapse rate, intensity of itching, and all other efficacy endpoints such as Dermatology Life Quality Index (DLQI) and children's DLQI (CDLQI) (26).

Tacrolimus 0.1% ointment, a TCI, has also been tested in a large, multicentric randomized double-blinded 12-month clinical trial involving 257 AD patients with mild, moderate and severe disease (5). Patients were randomized to twice-weekly proactive tacrolimus ointment or twice-weekly placebo after an initial flare treatment with twice-daily tacrolimus ointment. If a disease flare occurred, tacrolimus ointment b.i.d. was resumed for 1–6 weeks until the lesions were mostly cleared; then the patient returned to the original randomized treatment. Proactive therapy resulted in significantly less disease exacerbations (32 vs 66; $P < 0.001$), less disease exacerbation treatment days (12.4% vs 31.5%; $P < 0.001$), and increased the time until first relapse (142 days vs 15 days; $P < 0.001$), showing that a proactive approach can prevent, delay and reduce the occurrence of AD flares (5). Moreover, proactive treatment improved the quality of life significantly in patients with mild, moderate and severe symptoms and resulted in consumption of even less active drug in severe patients than the reactive regimen.

In conclusion, the patients and physicians should keep in mind that proactive therapy is an attempt to control residual disease with minimal use of anti-inflammatory drugs and not the application of an active drug to nonaffected skin. The choice of a proactive therapy regimen is favoured by immunological data, clinical efficacy data, quality of life data, and pharmacoeconomic data in the case of the more severely affected patients. In contrast, a reactive approach is better covered by the current licensing state of the anti-inflammatory topical drugs and is in line with the dermatological tradition. Though most clinical trial data has been collected using a twice-weekly approach, patient-specific tailoring of the proactive maintenance schedule (e.g. three times weekly in patients with severe symptoms and once weekly in patients with mild symptoms) may even increase the beneficial effects of the proactive approach. In addition, one might speculate that a proactive intervention in a very early stage of the disease might

even block the patient's sensitization process driven by a long-lasting atopic inflammation underneath the defective skin barrier (27), but this tempting hypothesis needs to be addressed in future studies.

In daily practice, the pros and cons of both approaches should be explained and discussed with each patient individually in order to reach a final decision together with the informed patient.

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