Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful?

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Background: Atopic dermatitis (AD) treatment is often initiated by symptoms or visible erythema. The role of induction of remission or treatment of inflammation that is not visible is unclear.

Objective: We investigated whether (1) the notion of subclinical inflammation is scientifically sound, (2) treatment corrects subclinical inflammation, and (3) different strategies for initial clearance of AD affect long-term disease control.

Methods: We conducted a systematic review based on searching MEDLINE, Embase, the Cochrane register of randomized controlled trials, and the Global Resource of Eczema Trials from inception to the end of October 2012.

Results: Twenty of 26 included studies presented evidence of subclinical inflammation, with a continuum of changes in skin barrier dysfunction, the proinflammatory cytokine milieu, and lymphocytic infiltration from normal-appearing skin to posttreatment lesional skin to active skin lesions in patients with AD. Such subclinical inflammation is improved, with proactive treatment aimed at maintaining remission. Failure to achieve control of AD symptoms with initial therapy was associated with a higher risk of relapse in 14 randomized controlled trials (fluticasone: risk ratio, 1.31; 95% CI, 1.02-1.68; tacrolimus: risk ratio, 1.36; 95% CI, 1.12-1.66). Three trials on systemic therapy/phototherapy suggested that induction of remission resulted in long-term remission without maintenance therapy in approximately 15% of patients.

Conclusion: Induction of remission followed by maintenance therapy might prove to be an integral part of a disease-modifying strategy for treating atopic diseases. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Eczema, atopic dermatitis, atopic eczema, induction of remission, subclinical inflammation, long-term management*

Abbreviations used
AD: Atopic dermatitis
EASI: Eczema Area Severity Index
IGA: Investigator's global assessment
PUVA: Psoralen plus UVA
RCT: Randomized controlled trial
RR: Risk ratio

Atopic dermatitis (AD) is a chronic inflammatory skin disease that can be treated with a range of pharmacologic agents.[1] However, it is often considered incurable because treatments are usually directed at relieving troublesome symptoms and skin appearance rather than trying to modify the natural course of disease.[2] Physicians and patients share the common goals of maintaining long-term remission and reducing disease burden by preventing further exacerbations and complications (ie, get control over the disease), yet it is not clear how these shared goals can be best achieved.

The use of proactive or "maintenance/weekend" therapy with topical corticosteroids or calcineurin inhibitors on 2 consecutive days each week at sites of previous lesions has been shown to produce a large clinical benefit in preventing flares in those with moderate-to-severe AD.[3] Most trials that assess such an approach start with a stabilization phase, which could be considered analogous to the "induction of remission" phase in other inflammatory diseases. For example, in the guidelines of the European Medicines Agency for development of new medicinal products for the treatment of ulcerative colitis, the definition of "remission" was described as "satisfactory response to the treatment," which should be followed by "maintenance of remission."[4]

There is an implicit belief that the purpose of induction of remission treatment is to treat the subclinical inflammation that persists after acute symptoms have resolved, although a precise definition of induction of remission in AD is not yet agreed. Our clinical experience of "getting control" before "keeping control" in children who present with AD that is out of control[5] has inspired us to explore whether the idea of induction of remission is useful in the management of AD. From a clinical standpoint, it would be useful to know whether there is benefit in continuing initial anti-inflammatory treatment 5 to 7 days beyond the point when most visible erythema and associated surface changes in AD have gone so that any remaining subclinical inflammation or "eczema under the skin" is also treated. In particular, it would be important to know whether a policy of treating inflammation "under the skin" could result in better subsequent disease control in terms of breaking the vicious cycle of inflammation barrier impairment and whether much longer induction of remission strategies with pharmacologic therapy can result in long-term remission.

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TABLE I. Interventional studies comparing lesional skin, nonlesional skin from patients with AD, and normal skin from nonatopic/healthy subjects

Reference	Patient no.	Diagnostic criteria	Intervention	Comparator	Sample
Bangert et al, 2011[8]	67 AD	Hanifin & Rajka	Topical pimecrolimus 1% cream twice daily for 3 wk	Vehicle	Biopsy
Caproni et al, 2007[9]	16 AD	Hanifin & Rajka	Topical tacrolimus 0.1% ointment twice daily for 3 wk	1% Hydrocortisone butyrate ointment twice daily for 3 wk	Biopsy
Simon et al, 2004[10]	10 patients with AD, 3 healthy control subjects	Hanifin & Rajka	Topical tacrolimus 0.1% ointment twice daily for 3 wk	No treatment for control group	Biopsy
Tintle et al, 2011[19]	12 patients with AD, 10 healthy control subjects	NR	Full-body NB-UVB 3 times weekly until clearance or up to 12 wk	No treatment for control group	Biopsy

NR, Not reported.

In this systematic review we summarized current evidence for induction of remission treatment as a potential integral part of a long-term disease modification strategy by aiming to answer the following 3 questions: (1) Is the notion of subclinical barrier dysfunction and subclinical inflammation scientifically sound when referring to normal-appearing atopic skin or treated areas of eczematous skin that are no longer visibly inflamed? (2) If so, has treatment been shown to correct such subclinical inflammation, and has it shown clinical efficacy? (3) Finally, do different strategies of induction of remission have an effect on long-term prognosis?

METHODS

We define subclinical inflammation as inflammation that is imperceptible to the naked eye and only detectable when using additional techniques, such as enhanced direct observation from advanced optics or skin biopsy and histology or indirectly by means of biomarkers. Subclinical inflammation is likely to precede and indeed follow the cessation of visible erythematous inflammation and symptoms and might exist, for example, in treated skin of patients with atopic eczema that is still lichenified but with no visible signs of erythema or surface change.

To investigate the first 2 questions, we conducted a systematic review of studies that investigated the difference between lesional skin, treated lesional skin, nonlesional normal-appearing skin from patients with AD, and normal skin from nonatopic/healthy subjects. We only considered studies with a control arm of normal-appearing skin from healthy/nonatopic subjects. Electronic searches were performed in MEDLINE and Embase through OVID and Scopus from inception to the end of October 2012. Search terms included the Cochrane Skin Group search strategy for AD[6] combined with "non-lesional," "non-involved," "uninvolved," and "subclinical inflammation."

For the third question, we systematically searched for randomized controlled trials (RCTs) with an initial stabilization treatment period (as an analogy for induction of remission) and a follow-up period of at least 12 weeks after the initial treatment period. Such studies also need to include an assessment of at least 1 of the following long-term outcomes: risk of relapse, time to first relapse, and disease-free days. Electronic searches were performed in MEDLINE, the Cochrane register of randomized controlled trials, and the Global Resource of Eczema Trials[1] by using the Cochrane Skin Group search strategy for AD/eczema. For each study, the quality of reporting of induction of remission therapy was assessed based on the following criteria: predefined remission criteria, total duration/dosage of initial therapy, blinded assessment of the duration of initial therapy, description of how discontinuation of initial therapy was decided, and extent of attrition bias. We anticipated that the data relating to the several questions posed would be quite heterogeneous and therefore planned a largely qualitative description of the data. In the event that we would find several studies that are sufficiently similar to each other in terms of patients, interventions, and outcomes when dealing with a specific question, we planned to enter the data into RevMan software and to pool the data using a random-effects model. In the event of significant heterogeneity ($I^2 > 50\%$), we planned to look for explanations for such heterogeneity by looking for differences in the intensity of the intervention, patient severity, and comparator. We did not plan any subgroup analysis.

For all unexplained attrition between the stabilization phase and the maintenance phase, we assumed a worst-case scenario by regarding such study participants as failing to achieve remission.

The online search was supplemented by review of the citations listed in all retrieved articles. All potential articles were scanned by the first author