What Is Meant by a “Flare” in Atopic Dermatitis?

A Systematic Review and Proposal

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Objective: To make preliminary recommendations for defining a flare of atopic dermatitis (AD) in clinical research based on a systematic review of the literature and experience in running clinical trials.

Data Sources: A sensitive electronic search of MEDLINE biographic database was conducted on April 19, 2005, using the following search terms: flare$, exacerbation$, relaps$, remission$, worse$, and *recurrence. The search was restricted to all prospective studies of AD in humans, using the Cochrane search terms for AD and prospective studies. In addition, we searched the literature on 3 chronic intermittent diseases (asthma, rheumatoid arthritis, and multiple sclerosis) to gain insight as to how other disciplines had tackled the definition of flares.

Data Synthesis: A total of 401 citations were reviewed, of which 16 articles (15 studies) were relevant. All were clinical trials. The definitions of disease flare or relapse in retrieved articles could be categorized into 3 broad themes: (1) composite definitions that include at least 2 different factors (eg, symptoms, severity duration, or treatment) (4 studies); (2) score thresholds or changes in severity scores (8 studies); and (3) behavioral definitions, such as the use of rescue therapy (3 studies). Only 1 investigative group (3 studies) used the same definition. None of the included studies were primarily designed to develop a definition of “flare.” Evidence from other disciplines suggested at least 2 measures—totally controlled weeks and well-controlled weeks from asthma research—that could be used successfully in AD research.

Conclusions: Defining an AD flare is a complex process, and this review has highlighted the need for standardization in defining measures of long-term disease control. We propose that a flare of AD be simply defined as an episode requiring escalation of treatment or seeking additional medical advice. Consideration should also be given to totally controlled weeks and well-controlled weeks to assess overall disease activity in patients with AD. Together, these definitions are intuitive, simple to use, and easy to understand. Future work is required to test the applicability of these recommendations in a variety of research settings.

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A TOPIC DERMATITIS (AD) IS a chronic relapsing and remitting disease characterized by flares or exacerbations over years. Despite this, most trials in AD have been of short duration (4-6 weeks), thereby concentrating on short-term disease control.1 More recent trials have begun to consider the issue of long-term control, with particular emphasis on the prevention of flares or relapses.2,3 This shift in focus has highlighted methodological issues regarding the definition of a flare, for which there is currently no clear guidance or agreement.

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METHODS

A detailed electronic search of the MEDLINE biographic database was done on April 19, 2005, using the following possible search terms: flare$, exacerbation$, relaps$, remission$, worse$, and *recurrence. The search was restricted to all prospective studies of AD in humans, using the
Cochrane search terms for AD and prospective studies. This included case series, case-control trials, and randomized controlled trials. The search resulted in 401 articles and was supplemented by reference checking of articles found in the primary search. Articles not written in English were first translated. An additional search of flare definitions in other chronic relapsing diseases such as asthma and rheumatoid arthritis was conducted to explore how other disciplines had tackled the problem of defining flares and relapses.

RESULTS

HOW OTHER RESEARCHERS HAVE DEFINED AD FLARES

The outcome of the search strategy is outlined in Figure 1.

The articles were either not relevant or did not attempt to define disease flares. In total, 16 articles (15 studies) measured disease exacerbation or flare. The criteria used in defining a flare varied widely but generally included some measure of worsening symptoms (7 of 15), the application of treatment (5 of 15), or duration of symptoms and/or treatment (6 of 15). All of the articles that provided a definition of disease flares were reports of clinical trials. No study was designed for the purposes of validating a definition of a disease flare in AD. Definitions of disease flare or relapse in the 15 trials could be categorized into 3 broad themes: (1) composite definitions, that is, describing a definition that includes at least 2 different factors (eg, symptoms, severity duration, or treatment) (4 trials); (2) score thresholds or changes in severity scores (8 trials); and (3) behavioral definitions, that is, defining a flare based on an action such as recourse to additional therapy or medical consultation (3 trials). A detailed summary of the 15 studies that have defined a disease flare is given in the Table and discussed in more detail in the following subsections according to the 3 broad categories.

Composite Definition of Flare

Four articles used a composite definition of AD flares; 3 of these articles derive from the same investigative group (the Multicenter Investigator Study Group) and the definitions are identical. Papp et al, Kapp et al, and Wahn et al defined flares as an Investigator Global Assessment (IGA) score of 4 or higher (range, 0-5), requiring corticosteroid therapy to begin within 3 days of the visit (either scheduled or unscheduled and prompted by a flare) and preceded by 7 days without corticosteroid use. Thomas et al defined relapse as a scratch score (range, 1-5) of more than 2 for at least 3 consecutive days.

Arbitrary Score Threshold or Change in Score

Eight articles provided a definition of disease flare based on a change in disease severity. Four groups of investigators used varying levels of change in the Scoring Atopic Dermatitis (SCORAD) score to define disease exacerbation. Other investigators have used the Three-Item Severity (TIS) score, the total body disease activity score, the IGA score, and the modified Costa scoring system (details are given in the Table). Three articles used operational definitions of relapse based solely on behavioral responses. The CASM-DE-01 Study Group defined relapse in their 2 articles as a period of at least 3 consecutive days in which moderately potent topical corticosteroid application was considered necessary (a named corticosteroid was selected for use in each participating country). In this group’s second article in 2004, they specified that the corticosteroids must be considered necessary by the investigator in their definition of flare, a point that was not clear in the 2002 article. Zaki et al stated that the need to use potent topical corticosteroids or further systemic treatment constituted a relapse.

Behavioral Definition

Three articles used operational definitions of relapse based solely on behavioral responses. The CASM-DE-01 Study Group defined relapse in their 2 articles as a period of at least 3 consecutive days in which moderately potent topical corticosteroid application was considered necessary (a named corticosteroid was selected for use in each participating country). In this group’s second article in 2004, they specified that the corticosteroids must be considered necessary by the investigator in their definition of flare, a point that was not clear in the 2002 article. Zaki et al stated that the need to use potent topical corticosteroids or further systemic treatment constituted a relapse.

LESSONS FROM OTHER CHRONIC DISEASES

The need to define flares and what constitutes disease control within the context of clinical research has been faced by those researching other chronically relapsing diseases. In some cases, consensus agreement had been achieved. For example, the Global Initiative for Asthma/National Institutes of Health guidelines have been adopted as a suitable definition of disease control for use in clinical trials of asthma. Similarly, the American College of Rheumatology has issued guidelines on the definition of disease improvement for use in trials of rheumatoid arthritis.

In asthma, the definitions include totally and well-controlled asthma weeks, based on symptoms, use of treatment and peak expiratory flow rate, emergency department visits, or medication-related adverse events over a 1-week period. Exacerbations are defined as a deterioration in asthma requiring treatment with an oral corticosteroid, an emergency department visit, or hospitalization. If the patient needs oral corticosteroid treatment for more than 10 consecutive days, the 11th day is
Table. Definitions of Flares of Atopic Dermatitis Used in Prospective Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Interventions</th>
<th>Follow-up</th>
<th>Single or Multiple Flares</th>
<th>Primary Outcome</th>
<th>Severity of AD</th>
<th>Definition of Flare Used</th>
<th>Symptoms/Signs of Flare</th>
<th>Treatment/Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papp et al.2004</td>
<td>Double-blind RCT of 1% pimecrolimus cream vs vehicle</td>
<td>1 y</td>
<td>Multiple</td>
<td>Composite Scales</td>
<td>Days of treatment with 1% pimecrolimus or 1% CS</td>
<td>Moderate or severe</td>
<td>IGA score ≥ 4; CS use for 3 d; CS-free for 7 d</td>
<td>No/Yes/Yes/Yes</td>
<td>Same methods as Kapp et al. and Wahn et al.5</td>
</tr>
<tr>
<td>Kapp et al.2002</td>
<td>Double-blind RCT of 1% pimecrolimus cream vs vehicle (CS for flares)</td>
<td>1 y</td>
<td>Multiple</td>
<td>Incidence of flares at 6 mo</td>
<td>Moderately severe</td>
<td>IGA score ≥ 4; CS use for 3 d; CS-free for 7 d</td>
<td>No/Yes/Yes/None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Wahn et al.2002</td>
<td>Double-blind RCT of 1% pimecrolimus cream vs vehicle (CS for flares)</td>
<td>1 y</td>
<td>Multiple</td>
<td>Ranked flares of AD in 6 mo</td>
<td>Moderately severe</td>
<td>IGA score ≥ 4; CS use for 3 d; CS-free for 7 d</td>
<td>No/Yes/Yes/None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Thomas et al.2002</td>
<td>Double-blind RCT of 0.1% betamethasone valerate for 3 d vs 1% hydrocortisone ointment for 7 d</td>
<td>18 wk</td>
<td>Multiple</td>
<td>No. of scratch-free days and No. of relapses</td>
<td>Mild and moderate AD</td>
<td>Scratch score ≥ 2 for 3 consecutive days</td>
<td>Yes/No/No/Yes</td>
<td>Assessed CS use but not in the definition of flare</td>
<td></td>
</tr>
<tr>
<td>George et al.1993</td>
<td>Open-label study: baseline, 12 wk; narrow-band UV-B (TL-01); 3 wk for 12 wk; follow-up, 24 wk</td>
<td>48 wk</td>
<td>Single</td>
<td>Arbitrary Score Thresholds</td>
<td>Severe</td>
<td>Severe relapse 70% prephototherapy Costa score</td>
<td>No/Yes/No/No</td>
<td>Assessed patient symptoms but not in definition of relapse</td>
<td></td>
</tr>
<tr>
<td>Granlund et al.2001</td>
<td>Open randomized parallel group trial; compared 8-wk treatment cycles of either cyclosporine or UV-A and UV-B</td>
<td>1 y</td>
<td>Multiple</td>
<td>No. of days in remission</td>
<td>Severe</td>
<td>SCORAD &gt; 50% baseline</td>
<td>Yes/Yes/No/No</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Bunikowski et al.2001</td>
<td>Open-label study of cyclosporine A</td>
<td>12 wk</td>
<td>Single</td>
<td>No. of days in remission</td>
<td>Moderate</td>
<td>SCORAD &gt; 50% baseline</td>
<td>Yes/Yes/No/No</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Atakan and Erdem,1998</td>
<td>Open-label study of Sandimmun Neoral®</td>
<td>36 wk</td>
<td>Single</td>
<td>SCORAD, cytokines IL-6, IL-8, and TNF-α</td>
<td>Moderate</td>
<td>SCORAD &gt; 50% baseline</td>
<td>Yes/Yes/No/No</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ehlers et al.2001</td>
<td>Double-blind sugar challenges</td>
<td>10 d</td>
<td>Single</td>
<td>Disease severity score</td>
<td>Moderate</td>
<td>SCORAD &gt; 50% baseline</td>
<td>Yes/Yes/No/No</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Birth-Jones et al.2003</td>
<td>Double-blind RCT of twice-weekly fluticasone propionate vs placebo base</td>
<td>20 wk</td>
<td>Single</td>
<td>Time to relapse</td>
<td>Moderate to severe</td>
<td>TIS score ≥ 4</td>
<td>No/Yes/No/No</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Granlund et al.1995</td>
<td>Open-label study: two 6-wk treatment periods of cyclosporine</td>
<td>32 wk</td>
<td>Multiple</td>
<td>Length of remission</td>
<td>Severe</td>
<td>Disease activity score &gt;75% baseline</td>
<td>No/Yes/No/No</td>
<td>Symptoms and steroid use recorded but not in definition of flare</td>
<td></td>
</tr>
<tr>
<td>Hanfin et al.2002</td>
<td>Open-label stabilization followed by double-blind maintenance RCT of twice-weekly 0.05% fluticasone propionate cream vs vehicle</td>
<td>48 wk</td>
<td>Single (withdrawn from study)</td>
<td>Risk of relapse in maintenance phase</td>
<td>Moderate to severe AD</td>
<td>IGA score ≥ 3 and score 2-3 for any 2 of erythema, itch, papulation/infiltration/edema</td>
<td>Yes/Yes/No/No</td>
<td>CS use recorded but not in definition of flare</td>
<td></td>
</tr>
<tr>
<td>Meurer et al.1992</td>
<td>Double-blind RCT of 1% pimecrolimus cream vs vehicle</td>
<td>24 wk</td>
<td>Multiple</td>
<td>No. (%) of days on which topical CS was used</td>
<td>Moderate to severe</td>
<td>Disease state requiring CS use for ≥3 d</td>
<td>No/Yes/Yes/Yes</td>
<td>Symptoms assessed but not in definition</td>
<td></td>
</tr>
<tr>
<td>Zaki et al.1996</td>
<td>Open-case series treated with cyclosporine</td>
<td>12 wk</td>
<td>Single</td>
<td>Response to treatment</td>
<td>Severe</td>
<td>Need to use potent topical CS/further systemic treatment</td>
<td>No/Yes/No/Yes</td>
<td>Some children part of multicenter study</td>
<td></td>
</tr>
<tr>
<td>Meurer et al.2004</td>
<td>Double-blind RCT of 1% pimecrolimus cream vs vehicle</td>
<td>24 wk</td>
<td>Multiple</td>
<td>No. (%) of days on which topical CS was used</td>
<td>Moderate to severe</td>
<td>IGA score ≥ 3 and score 2-3 for any 2 of erythema, itch, papulation/infiltration/edema</td>
<td>Yes/No/Yes/Yes</td>
<td>IGA score and pruritus rating also determined</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CS, corticosteroid; IGA, Investigator Global Assessment; max, maximum; RCT, randomized controlled trial; SCORAD, severity scoring of atopic dermatitis; TIS, Three-Item Severity; TNF-α, tumor necrosis factor α.

*Microemulsion formulation of cyclosporin (Novartis, East Hanover, NJ).
considered to be a second exacerbation. Thus, the definition of control incorporates duration, symptoms, medication use, peak expiratory flow rate, and need for further treatment.

In rheumatoid arthritis, the American College of Rheumatology and other groups have formulated well-established definitions of remission. The concept of a “flare” of rheumatoid arthritis does not appear to have been agreed as a consensus, with research mainly focusing on levels of disease activity. The definition of exacerbation or relapse in relation to rheumatoid arthritis as used in trials is usually based on a cutoff on an arbitrary remission score, but in some studies descriptive terminology has been used. In relation to multiple sclerosis, investigators have studied the concept of flares and a definition coined by Schumacker et al is widely used. This definition of relapse incorporates symptoms, signs, and duration. Some investigators have added arbitrary cutoffs on disability scales to this definition in an effort to incorporate an objective scoring system and improve the clarity of the definition.

STRENGTHS AND LIMITATIONS OF DIFFERENT APPROACHES TO DEFINING FLARES

Composite Definitions

Composite scales have emerged in the literature recently for AD. Their main advantage is the use of a multidimensional scale incorporating several factors, such as duration, symptoms, signs, and/or treatment. However, their increased complexity can lead to difficulties in interpretation, classification, and high proportions of missing data.

To illustrate some practical difficulties of using composite scales, we have used data from our own research. An exacerbation of disease (relapse) was defined as a daily itch score higher than 2 for 3 consecutive days (Figure 2A). This definition generally worked well, as illustrated in Figure 2A. However, during data analysis it became clear that rules were required for occasional cases. Figure 2B illustrates a situation in which a lengthy relapse was broken by a brief remission (2 days). Should this be classed as a single relapse or 2 relapses separated by a period of remission? (Single relapse [remission had to be sustained for at least 3 days for it to signify the end of a flare].) Similarly, if there is high disease activity throughout but never persisting for 3 consecutive days, should this be considered a relapse? (Figure 2C)?

Arbitrary Score Threshold

Most of the articles that used an arbitrary threshold to define a relapse used the patient’s disease severity compared with baseline. The advantage of this system is the clarity of the definition. However, in reality the baseline in a relapsing disease such as AD will fluctuate. If the patient’s disease is severe at baseline, they are unlikely to experience the percentage increase in score necessary for a relapse because of a “ceiling effect.” A further assumption is that the baseline represents “normal” or “stable disease,” which may not be the case unless the patient’s disease is deliberately stabilized prior to enrollment in the trial. Inclusion criteria, study population, and the use of a washout period will all affect baseline scores.

A further important issue with definitions of disease flare based on arbitrary score definitions is that it involves little or no input from the patient. While SCORAD incorporates patient symptoms (itch and sleep loss), some of the other scoring systems, such as TIS and Six-Area, Six-Sign Atopic Dermatitis (SASSAD), rely entirely on
A “flare” of AD is defined as an episode resulting in behavior such as requiring an escalation of treatment or seeking additional medical advice. This should be predefined by investigators at the outset of a study and will vary depending on the study in question. For instance, in a study of participants with mild AD, escalation to the use of topical corticosteroids might constitute a “flare,” in studies of moderate or severe AD, the need to use potent or superpotent topical corticosteroids or to see a primary care physician or dermatologist for disease worsening might be more appropriate. Different people will choose to respond to disease worsening in a variety of ways. The decision to escalate treatment or to seek further medical advice therefore becomes a useful surrogate for disease flare as perceived by the patient.

RECOMMENDATIONS

This review has highlighted some of the difficulties in defining a flare of AD and how others have tried to define AD flares. Little research has been done in this area, and there is currently no consensus definition of the best way to capture long-term control. Nevertheless, some broad recommendations regarding the definition of disease flares in AD can be made.

Definition of Flare

A definition of disease flare based on a behavioral response to disease activity (such as applying a potent topical corticosteroid or a visit to a health care professional) appears attractive. Such a definition incorporates the patient’s reaction to the status of their skin and may be less subjective than concepts such as reporting itch in a questionnaire. However, the decision to treat is governed by many more factors than simple disease activity. Habit may play a part, as does anxiety, parental instruction, personality, and treatment expectation. The adverse effects of topical corticosteroids are a particular concern for patients with AD, which means that those patients (or their caregivers in the case of children) who are worried about using topical corticosteroids may choose not to treat despite increased disease activity.

Behavioral Definition

A definition of disease flare based on a behavioral response to disease activity (such as applying a potent topical corticosteroid or a visit to a health care professional)
treatment,” as described in our definition of flare. Within the confines of a clinical trial, “rescue treatment” would usually be defined by the study protocol but could also include the study treatment itself if it is applied in response to changes in disease activity. A well-controlled week is one in which treatment has been applied for a period of 2 days or less and symptoms are controlled most of the time. Both these definitions are based on assessments over consecutive 7-day periods. Choosing treatment, symptoms, and duration as the components of these definitions, rather than signs, is pragmatically chosen to suit clinical research in which daily or weekly patient review is often impractical.

Including well-controlled weeks or flares as an outcome measure is not always useful in clinical trials. It is important to strike a balance between capturing meaningful outcomes that are understood by patients and clinicians (such as well-controlled weeks or flares) and using outcomes that are sufficiently sensitive to capture a difference in treatment response. To inform this decision process, a possible decision pathway has been outlined (Figure 4).

We have conducted a retrospective review of studies that were not primarily devised to define flares of AD. Our recommendations will therefore require further testing in clinical studies of AD.

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REFERENCES


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