Measurement of disease severity in cutaneous autoimmune diseases
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Abstract
The development of disease-specific outcome instruments for several autoimmune skin diseases including cutaneous lupus erythematosus (CLE), dermatomyositis, vitiligo, pemphigus and alopecia areata has facilitated the objective assessment of disease in clinical trials. Validation of these instruments provides reliable tools to measure disease severity and therapeutic effect in clinical studies. However, the existence of multiple outcome measures for each disease and the lack of uniformity between studies has created a challenge in comparing results across trials. Efforts to address this issue include the Core Outcome Measures in Effectiveness Trials (COMET) initiative and international meetings directed at reaching a consensus. Other challenges with the use of outcome measures include difficulties measuring change in mild disease, measuring response in topical studies, and capturing disease activity in skin with extensive post-inflamatory hyperpigmentation.

The importance of outcome measures for cutaneous autoimmune disease
Until recently, there has been a near-absence of clinical studies in autoimmune skin diseases. The understanding of disease progression and development of novel therapeutic options for cutaneous autoimmune diseases, including CLE, dermatomyositis, morphea, vitiligo, pemphigus, and bullous pemphigoid, is facilitated by the recent development and efforts to validate outcome instruments specific to each of these conditions. Validated disease severity measures allow objective assessment of disease in clinical practice, translational research, and comparative trials. More global measures of disease severity, like those required for studies of systemic lupus erythematosus (SLE) introduce the challenge of capturing improvement in a single-organ system [1]. Skin-specific outcome measures have the potential to more accurately assess the efficacy of skin-directed therapies. Successful development of these measures requires consensus among physicians to prevent a mushrooming of indices, thus facilitating comparison in clinical practice outcomes and clinical trials.

Two systematic reviews noted the use of 25 different outcome measures [2] and 11 different instruments [3] in randomized controlled trials of vitiligo treatments. This lack of uniformity contributes to the challenge of comparing trials and making clinical decisions.

Many aspects of skin disease can be measured, but skin-specific outcome measures need only include the few cutaneous manifestations that are both reliable and characteristic of disease activity. Efforts to reach a consensus on the most appropriate tools to measure cutaneous autoimmune disease have included discussions at the First International Conference on CLE [4], the Rheumatologic Dermatology Society, and the International Pemphigus Committee [5]. A similar exchange of ideas is taking place on a larger scale through the Harmonizing Outcome Measures for Eczema (HOME) [6] and the COMET initiative [7].

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) resulted from an iterative process
among several rheumatologists and dermatologists [8]. Feedback and suggestions were implemented after use of earlier versions by the group [8]. Similarly, the Pemphigus Disease Area Index (PDAI) and Bullous Pemphigoid Disease Area Index (BPDAI) were developed by an international group of bullous disease experts seeking reliable measures to compare outcomes [9].

Features of a reliable clinical outcome measure include credibility, comprehensiveness, sensitivity, accuracy, construct validity, and feasibility [10]. Validation of disease severity measures also requires consideration of inter-rater and intra-rater reliability as well as responsiveness. This process, largely completed with the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) [13-16], the PDAI [17,18] and the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) [19,20]. These instruments distinguish between activity and damage to avoid paradoxical stability in instances when disease activity improves and damage persists. The notion of evaluating skin disease in several anatomic areas rather than approximating percentage of body surface area affected encourages examination of the whole body while optimizing the ability to quantify severity. Other instruments based on measuring surface area may be difficult to use in patients with diseases that frequently involve small surface areas [13,17].

**Patient care and the patient perspective**

Given that medical specialists who are not dermatologists care for patients with cutaneous autoimmune conditions, it is desirable that disease-specific outcome measures be readily extended for their use. Krathen et al. evaluated the validity of the CLASI among rheumatologists and found excellent inter- and intra-rater reliability and a strong correlation with CLASI reliability among dermatologists [21]. This study highlights the importance of appropriate attribution of skin findings in order to maintain reproducibility and appropriate use of these tools by physicians of different disciplines.

Validation of the CLASI has made it available for use in studies evaluating the efficacy of various therapeutic options for CLE [11,22-29]. As validated outcome measures become available for other conditions, it is hoped that similar advances will be made, facilitating greater numbers of studies that develop evidence for treatment efficacy.

Autoimmune skin diseases are associated with severely impaired quality of life, as demonstrated in recent studies of CLE and dermatomyositis [30,31]. Several studies have investigated the relationship between quality of life and disease severity in cutaneous autoimmune diseases [12,32,33]. While it is important to maintain the separation of physician- and patient-derived scores [34], patient-derived outcome measures can contribute to the assessment of overall disease. Patient input may be obtained using visual analogue scales for pain and itch, health related quality of life questionnaires focusing on the skin, such as the Skindex and Dermatology Life Quality Index (DLQI), or on the disease impact overall, with the Short Form 36 (SF-36) and the Health Assessment Questionnaire-Disability Index (HAQ-DI). The Alopecia Areata Quality of Life Index (AA-QLI) is a disease-specific questionnaire developed to evaluate the impact of alopecia areata on quality of life, which was found to have greater specificity [35]. These patient-reported outcomes contribute to the measurement of disease severity in cutaneous autoimmune diseases.

**Translation from clinical practice to bench research**

Another relationship, the correlation of clinical response with biomarkers, is becoming an important way to elucidate the molecular pathways that underlie the pathogenesis of cutaneous autoimmune disease and provide an independent and potentially early evaluation of the efficacy of therapy. This past year, Braunstein et al. demonstrated increased expression of five interferon (INF)-regulated genes in patients with CLE that correlated with cutaneous disease activity, as determined by the CLASI [36]. These results suggest that the presence of an interface dermatitis in specific subtypes of CLE, namely discoid and subacute CLE, likely share some common inflammatory pathways with SLE [36]. Additionally, Oh et al. have shown that INF\(\alpha\) and another cytokine, interleukin-17, positively correlate with the CLASI score, indicating the role of INF\(\alpha\) in the pathogenesis of CLE [37]. Another study from Nabatian et al. showed positive correlation with tumor necrosis factor (TNF)-\(\alpha\) release by cultured peripheral blood mononuclear cells and disease severity in discoid lupus erythematosus, as measured by the CLASI [38]. By understanding the molecular pathways that correlate with clinical manifestation of disease, it may be possible to develop more targeted treatments for cutaneous autoimmune diseases, as well as identify biomarkers that may be used to evaluate disease response to therapy. This new knowledge may also allow mechanistic studies about how current treatments, such as antimalarials, work and why certain patients are refractory to treatment [39,40].

**Hitting the floor: disease severity in clinical trials**

The development and validation of outcome instruments permits objective measurement of disease severity, a necessary feature that allows the results of clinical trials...
to be accurately interpreted and compared. Difficulties have been noted in measuring and validating change in mild cutaneous autoimmune disease and are largely attributed to a statistical concept known as the floor effect [41-43]. Floor effect describes a situation in which the data measured cannot assume a value lower than a particular number, i.e. "the floor" and much of the data is close to this threshold [43]. In other words, mild disease has less room for improvement than severe disease. Thus, measuring change in mild disease with an outcome instrument can be problematic. The Psoriasis Area and Severity Index (PASI) and Psoriasis Disability Index, for example, have both shown significant floor effect [41,42]. This necessitates the use of patients with moderate to severe disease in clinical trials to demonstrate efficacy of therapeutic agents [44-46].

**New challenges and new approaches**

While much progress has been made in quantifying disease severity in autoimmunity, there are still questions that cannot be easily answered with an outcome instrument. Though focusing on populations with severe and moderate disease in clinical trials avoids negative results due to the floor effect, the problem of effectively and objectively measuring clinically mild disease remains [41-43]. Measurement of disease response using validated outcome instruments in topical studies has also proved difficult, as many outcome measures are inadequate to assess a single lesion or clinical disease that only affects a small area of skin, especially those that use body surface area as a parameter [13,17,18,47,48]. Recently, Erceg et al. showed promise for pulsed dye laser therapy in discoid cutaneous lupus erythematosus using the CLASI, but excluding its disease area component, as a validated instrument to measure response in single lesions [23]. Change in disease activity was reflected in the CLASI score [23], indicating that the CLASI may be more sensitive than other external measures, such as visual analogue scale activity or Likert scores, in evaluating mild disease and single lesions. Chang et al. also indicate that the CLASI may be more sensitive in evaluating mild disease in their statistical analysis [43]. However, this is hard to prove without more sensitive gold standards to evaluate mild disease [43,23].

The objective and reliable measurement of erythema in darker skin tones also remains a challenge. Frequently, one can distinguish activity and damage in the same lesion, with erythema determined visually as pinkness or redness in comparison to background skin. However, when hyperpigmentation is marked and overlaps with the erythema it can be difficult to evaluate the erythema [49]. Objective methods have been explored, including use of diffuse reflectance spectroscopy and colorimetry to measure erythema *in vivo* [49,50]. These types of solutions come with their own problems including variables like probe-skin contact and temperature, and appropriate operational training [49]. Some studies have suggested that visual determination of erythema correlates with objective measures [51-53]. Specifically, studies in Japanese subjects suggest that responsiveness can be demonstrated visually [54], but additional studies in dark skin are needed.

In the past few years, great strides have been made in understanding disease progression and developing therapeutic solutions for cutaneous autoimmune diseases through the utilization of validated outcome instruments. Clinical trials and translational research have emerged from the shared efforts of physicians to reach a consensus on the most appropriate tools to assess
cutaneous disease. Though challenges still remain, including assessing mild disease and objectively characterizing erythema, the implementation of outcome instruments has offered a sensitive and accurate way to discuss cutaneous autoimmune diseases over many studies in many disciplines.

**Abbreviations**
AA-QLI, Alopecia Areata Quality of Life Index; BPDAL, Bullous Pemphigoid Disease Area Index; CDASIL, Cutaneous Dermatomyositis Disease Area and Severity Index; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLE, cutaneous lupus erythematosus; COMET, Core Outcome Measures in Effectiveness Trials; DLQI, Dermatology Life Quality Index; HOME, Harmonizing Outcome Measures for Eczema; INF, interferon; LoSCAT, Localized Scleroderma Cutaneous Assessment Tool; PASI, Psoriasis Area and Severity Index; PDAI, Pemphigus Disease Area Index; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

**Disclosure**
Victoria Werth developed the CLASI and CDASI, and the copyright is owned by the University of Pennsylvania.

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