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How to measure itch in atopic dermatitis?

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Linked Article: Silverberg *et al.* Br J Dermatol 2020; **183**:891–898.

What is the best way to measure the negative influence of a disease on an individual? For many illnesses this is currently investigated in working groups that involve professionals and patients to obtain consensus. For atopic dermatitis (AD), the Harmonizing Outcome Measurements in Eczema (HOME) group ponders this question.[1] The group initially recommended the use of the Patient-Oriented Eczema Measure (POEM) for measurement of AD symptoms in clinical trials.[2] However, itch is a hallmark symptom of AD, and it has been shown that a simple singe-item numerical rating scale (NRS) for itch correlates equally to or even more strongly with a general measure of AD severity (the question 'Would you describe your atopic dermatitis or eczema as mild, moderate, or severe?') than does the POEM.[3,4] Following a validation study by Yosipovitch *et al.*, an 11-point NRS-itch, specifying a recall period of 24 hours with a qualifier for itch, the peak (worst) itch, was incorporated into the HOME core outcome set for trials.[5,6] The newly formed 'HOME in clinical practice initiative' also intends to address itch. However, before their most recently published meeting, peer-reviewed validation studies for an NRS-itch instrument in AD had not been published.[7]

In this issue of the *BJD*, Silverberg *et al.* report on the measurement properties of the Patient-Reported Outcomes Information System (PROMIS®) Itch Questionnaire (PIQ)–itch severity assessment.[8] They studied an NRS and verbal rating scale (VRS) for worst and average itch in the past 7 days, along with an assessment of frequency of itch during that period. From their comprehensive and methodologically sound validation study, the authors conclude that NRS and VRS for worst and average itch, and frequency of itch each have slight advantages over the other for different aspects of validity. They suggest that NRS for 'worst itch' is the preferred question to be used as a standalone, combined with frequency of itch and/or VRS for 'worst itch' wherever feasible.

The most profound differences between the studies of Yosipovitch *et al.* and Silverberg *et al.* are the recall period (24 hours vs. 7 days) and the fact that participants indicated a preference for peak/worst itch, as opposed to average itch. Also, the study group differed: patients included in dupilumab trials for moderate-to-severe AD vs. patients with all AD severities treated according to daily practice. This means that the studies are not directly comparable. Therefore, choosing one instrument over the other is difficult. For the 'HOME in clinical practice initiative' this is not an issue. The initiative aims to create a 'pick-and-choose' list of properly validated and feasible instruments to use for the measurement of a particular domain, which may very well result in the inclusion of both instruments in the clinical practice set. An important addition to this is that potential users should be guided to use the set of available interpretability values (severity strata and minimal clinically important difference/minimal important change) that matches the NRS of their choice.

Meanwhile, although the subjective experience of the patient is important, objective measurement should certainly not be ruled out as a feasible option to assess itch, particularly in clinical trials. Tools within the realms of acoustic surveillance, wrist actigraphy, smart devices and neurological imaging all have their pros and cons. Further development is needed, as well as the identification of biomarkers that correlate with itch.[9]

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Is targeting circulating T blood cells a therapeutic option for vitiligo?

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Vitiligo is an autoimmune depigmenting skin disorder that results from the loss of melanocytes due to an altered proportion and/or function of effector and regulatory T cells.[1,2] More specifically, the T-helper/cytotoxic T-cell (Th)1/(Tc)1 immune response is affected by an increased production of interferon (IFN)-γ and tumour necrosis factor (TNF)-α.

In this issue of the *BJD*, Martins *et al.* reaffirm the role of Th1 and Tc1 cell subsets in vitiligo disease and its production of both IFN-γ and TNF-α.[3] Furthermore, their results show that the frequency of $CD4^+$ and $CD8^+$ circulating Th17/Tc17, Th1/Th17 and Tc1/Tc17 effector memory T-cell subsets is significantly lower in patients with vitiligo (both with stable and active disease) and psoriasis, in comparison with healthy donors. These findings suggest a possible migration of distinct T-cell subsets from the blood into the skin. The same authors have previously shown that vitiligo perilesional skin is imprinted with pathogenic $CD8^+$ resident memory T cells (T_{RM}).[4] Future studies should investigate which blood memory T-cell subsets ultimately differentiate into vitiligo-pathogenic T_{RM} cells.

Many studies on patients with vitiligo focus exclusively on patients with active disease. However, Martins *et al.*[3] show that the same immune response is found in the blood of patients with active and stable disease. Previous studies have shown the presence of T_{RM} cells in vitiligo skin,[4–6] which are likely involved during flares, as previously shown in psoriasis.[7]

The precise role of circulatory Th1/Th17, Tc1/Tc17 and Th17 cells and the production of interleukin (IL)-17 in patients with vitiligo remains unclear. Studies have shown increased IL-17 expression both in blood and perilesional skin of patients with vitiligo,[8] and serum level of IL-17 correlated with disease activity,[9] while other studies have observed a similar frequency of IL-17-producing CD4 and CD8 T cells in vitiligo skin and skin from unaffected individuals.[4] A single-arm pilot study using secukinumab showed that directly targeting the IL-17 pathway is not a reliable strategy in vitiligo.[10] The work of Martins *et al.*[3] raises important questions, such as whether pathogenic IFN-γ-producing cells also secrete IL-17 in patients with vitiligo or whether the IL-17 production is a consequence of the activation of Th1/Th17 or Tc1/Tc17 cells.

Together, these findings indicate that targeting blood-specific T-cell subsets that migrate into the skin of patients with vitiligo could prevent the flare of the disease. Nevertheless, further studies will have to elucidate which circulating skin-homing T-cell subsets truly cause the cutaneous changes seen in patients with vitiligo.

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