

Journal Pre-proof

Reversal of the disease signature in prurigo nodularis by blocking the itch cytokine

Enikő Sonkoly, MD PhD

PII: S0091-6749(22)00227-5

DOI: <https://doi.org/10.1016/j.jaci.2022.02.009>

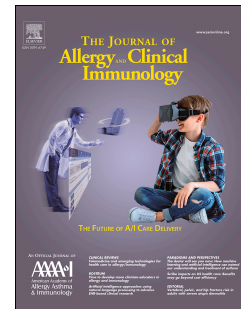
Reference: YMAI 15471

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 3 February 2022

Revised Date: 11 February 2022

Accepted Date: 16 February 2022



Please cite this article as: Sonkoly E, Reversal of the disease signature in prurigo nodularis by blocking the itch cytokine, *Journal of Allergy and Clinical Immunology* (2022), doi: <https://doi.org/10.1016/j.jaci.2022.02.009>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

Reversal of the disease signature in prurigo nodularis by blocking the itch cytokine

Enikő Sonkoly, MD PhD^{1,2*}

¹ Department of Medical Sciences, Uppsala University, Uppsala, Sweden

² Dermatology and Venereology Division, Department of Medicine Solna, Karolinska Institutet, Solna, Sweden

*Corresponding author: Enikő Sonkoly, Uppsala University, Department of Medical Sciences, Akademiska sjukhuset, entrance 40, 5th floor, SE-751 85 Uppsala, Sweden; Phone: +46 73 0770374; email: eniko.sonkoly@medsci.uu.se

Keywords: Prurigo nodularis, itch, IL-31, IL-31RA, inflammation, transcriptome

Conflict of interest: ES is participating in a multicenter phase 3 study of nemolizumab in patients with prurigo nodularis (Galderma OLYMPIA1).

Acknowledgements: ES is supported by the Swedish Research Council (Vetenskapsrådet).

Word count: 1249

EDITORIAL

Prurigo nodularis (PN), or chronic prurigo of nodular type, is one of the most pruritic chronic skin diseases ¹. PN patients experience an intractable and severe itch that has a profound negative impact on their psychological wellbeing as it interferes with their sleep and daily activities ^{1, 2}. A subset of PN patients have an atopic background (11%-46.3%) ^{3, 4}, and other potential underlying factors have been identified including dermatologic and non-dermatologic diseases ⁴. Irrespective of the initiating factor, a vicious itch-scratch cycle develops, leading to the appearance of pruritic, hyperkeratotic, excoriated nodules. Breaking the itch-scratch cycle in PN represents a significant challenge and in the absence of FDA-approved treatments, numerous off-label treatments have been tested. However, these generally have a low success rate ², causing frustration for patients as well as treating physicians. With new targeted drugs on the horizon, this is about to change ².

The development of effective treatments has been hindered by gaps in our knowledge about the molecular events leading to and sustaining pruritus in PN. Earlier studies suggested neural dysregulation, inflammation, and aberrant keratinocyte functions as the main pathogenetic components of PN ^{2, 5}. One important piece of the PN-puzzle has been the identification of a connection between inflammation and itch. The discovery that IL-31, the “itch cytokine” mainly produced by immune cells, acts directly on neural cells to induce itch, has brought neuro-immune interactions into the spotlight ^{6, 7}. IL-31 belongs to the IL-6 cytokine family and can be produced by several cell types, although the main source at present is thought to be Th2 cells ⁶. Among a range of inflammatory skin diseases, IL-31 was shown to have the highest expression in PN ⁷. IL-31 binds to its heterodimeric receptor composed of an IL-31RA-chain and an oncostatin M receptor (OSMR) β -chain, and activates the JAK/STAT pathway. Since OSMR is broadly expressed, the factor restricting responsiveness to IL-31 is the expression of IL-31RA-subunit. IL-31RA is expressed on sensory neurons in the dorsal root ganglia, allowing IL-31 to directly act on the nervous system to induce pruritus. In addition, IL-31RA is expressed on epithelial cells in which IL-31 can induce itch mediators, as well as on immune cells and stromal cells, allowing a multifaceted action in the skin.

In a recent issue of the *Journal of Allergy and Clinical Immunology*, Tsoi et al. reports detailed molecular characterization of lesional vs. nonlesional skin of patients with moderate to severe PN enrolled in a recent phase 2 trial of nemolizumab, a humanized IgG2 monoclonal antibody directed against IL31RA ⁸, and show partial reversion of PN-associated transcriptome changes after 12 weeks of treatment nemolizumab ⁹. A high number of differentially expressed genes

(>5000) were identified in PN lesions, many of them related to epidermal differentiation, immunological changes, and remodeling. Moreover, a complex immunological landscape emerged with a mixture of IL-31-, Th2- and Th17 signatures, as well as type I- and type II-IFN responses. Surprisingly, the immune-related gene expression landscape of PN displayed more similarities with psoriasis than with atopic dermatitis⁴. Although these findings are somewhat surprising, they are supported by recent findings by Belzberg et al., analyzing transcriptomic profiles in PN patients mainly of African American origin⁵. Importantly, despite the above-mentioned similarities, IL-17A - the prototype psoriasis cytokine - was not elevated in any of the two studies^{5,9}. As some of the psoriasis-associated genes (e.g. K6/16, IL-36) also belong to a wound-healing signature, part of this signature might also reflect a response to physical trauma and inflammation in excoriated nodules.

Another interesting aspect of the study is that the Th2 cytokines tightly associated with atopic dermatitis, IL-4 and IL-13, were not found to be significantly upregulated in PN lesions as one may have hypothesized considering that a subset of PN patients have atopic dermatitis^{3,4} and the observation that IL-4/13R inhibition by dupilumab has been shown to be efficient in PN patients in several case reports⁴. Importantly, however, IL-4R was upregulated and the “interleukin 4- and 13-signaling” was enriched in PN, suggesting the involvement of Th2 immunity in the pathogenesis of PN. This is also in agreement with the study by Belzberg et al⁵, where a Th2 signature was observed in a subset of PN patients of European origin. These results, also considering ongoing clinical trials with dupilumab for PN², warrant for further investigations of the involvement of Th2 immunity in PN.

An important question answered by this new study is whether inhibition of IL-31RA can reverse the extensive gene expression changes in PN. Results presented by Tsoi et al. indicate that inhibition of IL-31RA not only effectively decreases itch but can also partially reverse the PN signature after 12 weeks of treatment. As expected, IL-31-responses were consistently decreased by nemolizumab. Of note, among the genes specifically normalized by nemolizumab, the most profound effects were found on *IL22*, and *IL-36A/G*. IL-22 has been implicated as an important cytokine in PN, and its decreased levels may contribute to normalization of epidermal thickening⁵, while IL-36 is involved in an autoinflammatory loop in keratinocytes and its decreased levels may contribute to decreased inflammation and neutrophil infiltration. In addition, genes involved in cell proliferation/differentiation, and IL-4- and IL-13-signaling were specifically decreased by nemolizumab. Notably, a set of genes in the PN signature, such as those associated with basal keratinocytes, were also reversed in the placebo group. While

pruritus is commonly reduced to some extent by placebo in clinical trials, it is noteworthy that partial normalization of gene expression occurs in this group, perhaps as a result of a - previously underestimated - neuro-epithelial communication.

Altogether, results presented in this study provide valuable insights into the pathogenesis of PN and the role of IL-31RA/ IL-31-signaling in the disease. The broad effects of IL-31RA inhibition on gene expression are consistent with multiple effects of IL-31 on inflammation, itch and epidermal functions ⁶, and with the known distribution of IL-31RA being expressed on keratinocytes, stromal cells, and immune cells, in addition to neurons ⁶. The observed effects of IL-31RA inhibition can thus be mediated through inhibition of IL-31 responses in a range of cell types.

Some questions to be addressed in future studies include the transcriptional/immunological heterogeneity of PN. Similar to atopic dermatitis, showing an immunological heterogeneity among ethnic groups, there are some indications for an ethnic heterogeneity in PN, which could be further explored ^{3,5}. Another open question is whether PN patients with or without associated atopy differ in their immunological profiles, even though the epidermal barrier impairment has been shown to be similar in these groups¹⁰, and whether such differences could direct therapy decisions. While the limited number of patients has precluded the identification of transcriptional changes potentially correlating with therapy response, this would be of interest to explore in the future. Finally, further studies would be needed to identify the contribution of different cell types to nemolizumab-action, as well as the dynamics of the response, to understand the primary and secondary changes upon IL-31RA inhibition, and the durability of the response, clinically and molecularly.

The results of Tsoi et al outline PN as a disease with neuroimmune alterations characterized by inflammation, epidermal alterations, fibrosis, and pruritus. The effects of IL-31RA-inhibition on the PN transcriptome confirm the pivotal role of the “itch cytokine” in the pathological neuroimmune circuits that sustain PN. If the revolutionary approach to interrupt pathways of communication between the immune system and the nervous system will hold up in the future, then patients with PN will finally have an effective remedy.

REFERENCES

1. Steinke S, Zeidler C, Riepe C, Bruland P, Soto-Rey I, Storck M, et al. Humanistic burden of chronic pruritus in patients with inflammatory dermatoses: Results of the European Academy of Dermatology and Venereology Network on Assessment of Severity and Burden of Pruritus (PruNet) cross-sectional trial. *J Am Acad Dermatol* 2018; 79:457-63 e5.
2. Williams KA, Huang AH, Belzberg M, Kwatra SG. Prurigo nodularis: Pathogenesis and management. *J Am Acad Dermatol* 2020; 83:1567-75.
3. Boozalis E, Tang O, Patel S, Semenov YR, Pereira MP, Stander S, et al. Ethnic differences and comorbidities of 909 prurigo nodularis patients. *J Am Acad Dermatol* 2018; 79:714-9 e3.
4. Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Stander S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol* 2013; 27:550-7.
5. Belzberg M, Alphonse MP, Brown I, Williams KA, Khanna R, Ho B, et al. Prurigo Nodularis Is Characterized by Systemic and Cutaneous T Helper 22 Immune Polarization. *J Invest Dermatol* 2021; 141:2208-18 e14.
6. Nemmer JM, Kuchner M, Datsi A, Olah P, Julia V, Raap U, et al. Interleukin-31 Signaling Bridges the Gap Between Immune Cells, the Nervous System and Epithelial Tissues. *Front Med (Lausanne)* 2021; 8:639097.
7. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; 117:411-7.
8. Stander S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, et al. Trial of Nemolizumab in Moderate-to-Severe Prurigo Nodularis. *N Engl J Med* 2020; 382:706-16.
9. Tsoi LC, Hacini-Rachinel F, Fogel P, Rousseau F, Xing X, Patrick MT, et al. Transcriptomic characterization of prurigo nodularis and the therapeutic response to nemolizumab. *J Allergy Clin Immunol* 2021.
10. Folster-Holst R, Reimer R, Neumann C, Proksch E, Rodriguez E, Weidinger S, et al. Comparison of Epidermal Barrier Integrity in Adults with Classic Atopic Dermatitis, Atopic Prurigo and Non-Atopic Prurigo Nodularis. *Biology (Basel)* 2021; 10.

FIGURE LEGENDS

Figure 1. Inhibition of IL-31RA by nemolizumab improves the PN transcriptomic signature associated with pruritus, epidermal functions, inflammation and remodeling. In the study of Tsoi et al, comparison of PN lesional vs. nonlesional skin revealed transcriptomic changes related to pruritus, keratinocyte proliferation/differentiation, inflammation, and tissue remodeling - processes that have been associated with IL-31 action in the skin. Inhibition of IL-31 signaling by nemolizumab, an antibody targeting IL-31RA, leads to partial reversion of the PN transcriptomic signature related to these biological processes. These results identify IL-31 signaling as a central hub in the pathogenesis of PN.

