IL-31 is Implicated in the Pathogenesis of Prurigo Nodularis, a Chronic Pruritic Skin Disease that can Exist Irrespective of Co-morbid Conditions (LOTUS-PN Study)

Poster P1566

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BACKGROUND

- Prurigo nodularis (PN, or chronic nodular prurigo) is a chronic skin disease of unknown etiology characterized by symmetrically-distributed, intensely-pruritic hyperkeratotic nodules. Comorbidities featuring chronic pruritus are implicated in PN pathogenesis by initiating the itch-scratch cycle leading to nodule formation
- The role of these co-morbidities in PN pathogenesis has not been elucidated
- IL-31, an inflammatory cytokine and a known pruritogen, has been implicated in PN, but its role in the mechanism of disease in PN is not yet understood
- Oncostatin M receptor β (OSMRβ) is the shared receptor subunit for interleukin 31 (IL-31) and oncostatin M (OSM) signaling. These cytokines play an important role in pruritus, inflammation, hyperkeratosis, and fibrosis (Figure 1), all of which occur in PN[1-11]
- PN carries a high unmet medical need, as the intense itching and ensuing lesions lead to sleep loss, embarrassment, anxiety, and depression[12, 13]
- Currently, there are no approved treatments for PN
- Herein we report findings from the LOngitudinal Trial to Understand Symptomatology in Prurigo Nodularis (LOTUS-PN), the first comprehensive, longitudinal observational study in PN

OBJECTIVES

- **LOTUS-PN** was a prospective, 12-month longitudinal/observational study conducted in the United States, Germany and Poland to investigate the pathophysiology of PN
- The principal objectives of the LOTUS-PN study were
  - Collect patient demographics and medical history, humanistic (patient-reported) outcomes, clinical (physician-reported) outcomes, and mechanistic biomarkers in patients with prurigo nodularis (PN) at baseline and up to a 12-month observation window,
  - Describe patient subsets, disease phenotypes and real-world treatment patterns of PN,
  - Understand inter-patient and intra-patient variability over time in outcomes measures, biomarkers, and treatment responsiveness,
  - Examine potential correlations between humanistic and clinical outcomes measures, biomarkers, disease phenotypes/patient subsets and treatment responsiveness.

Figure 1. IL-31 and OSM Receptor Signaling

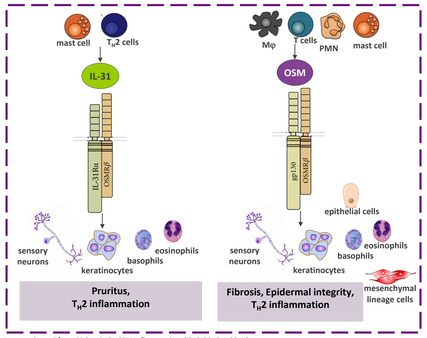


Image adapted from Richards C. *ISRN Inflammation*. 2013;2013:1-23.16.
gp, glycoprotein; IL-31, interleukin 31; IL-31Rα, interleukin 31 receptor α; LIF, leukemia inhibitory factor; LIFR, LIF receptor; OSM, oncostatin M; OSMRβ, oncostatin M receptor β; PMN, polymorphonuclear cells; T_H2, T helper cell type 2.

METHODS

Design

- Eligible patients were adults ≥18 years of age with a diagnosis of PN (new or established) Diverse etiologies were enrolled (e.g., atopic, gastrointestinal, hematologic, infectious, renal disease)
- No investigational drug was administered; patients received standard of care treatment deemed appropriate by their investigator physician
- This study assessed patients at baseline and at monthly scheduled intervals, as well as during unscheduled visits for disease flare for a period of up to 12 months

Biopsy and Plasma Samples

- Lesional (LS) and non-lesional (NL) skin biopsies and plasma samples were collected from PN patients
  - Skin biopsies were explored for assessment of various biomarkers, such as cytokines, cytokine receptors, chemokines, and chemokine receptors, as well as genes involved in epidermal integrity, keratinocyte activation, various forms of inflammation and fibrosis

Assessments

- Messenger RNA (mRNA) expression of IL-31, OSM, IL-31Rα, and OSMRβ was measured by quantitative real-time polymerase chain reaction (qRT-PCR) using a TaqMan Low-Density Array
- Protein expression of IL-31, OSM, IL-31Rα, and OSMRβ in tissues was analyzed using IHC
- IL-31 protein levels from plasma samples were measured using Single Molecule Array (Simoa)
- The following measurements per target molecule were taken
  - IHC of skin tissue (tissue staining for target molecules was scored as negative, questionable, positive, or strong positive)
  - Target molecule expression levels represented by IHC score

RESULTS

- Between September 2017 and May 2018, 54 patients were enrolled at 11 sites in US, Germany and Poland
- The mean age was 53.8, 57% of the patients were female, and 28% were black or African American.

Table 1. Demographics

	Patients N=54
Age, mean (SD), years	53.8 (12.9)
Female, n (%)	31 (57)
Race, n (%)	
White	35 (65)
Black or African American	15 (28)
Asian	1 (2)
American Indian or Alaska Native	1 (2)
Native Hawaiian or Other Pacific Islander	0
Multiple	0
Other	2 (4)
Ethnicity, n (%)	
Hispanic or Latino	2 (4)
Not Hispanic or Latino	51 (94)
Unknown	1 (2)
Country of residence, n (%)	
Germany	15 (28)
Poland	5 (9)
United States	34 (63)

Majority of PN Patients had no Causally-Related Underlying Comorbidities

- A majority of patients (n=35, 65%) had PN with no identified underlying comorbidities (UC) (4 patients with no other medical condition and 31 patients with other medical condition(s) not considered causally-related [PN + no UC])
- The remaining 19 (35%) participants had underlying medical conditions that were considered causally-related (PN + UC):

Causally-Related Underlying Medical Condition	Participants/ Each Condition (%)
Atopic Dermatitis 6 (11%)	6 (11%)
Depression, Hypothyroidism	3 (6%)
Diabetes, Bipolar Disorder, Hepatitis C, HIV/AIDS, Chronic Renal Failure	2 (4%)
Lupus, Anxiety, Allergic Contact Dermatitis, Obesity	1 (2%)
Other	9 (18%)

Figure 2. Underlying Comorbidities (UC)

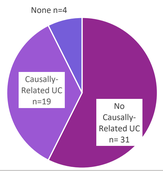
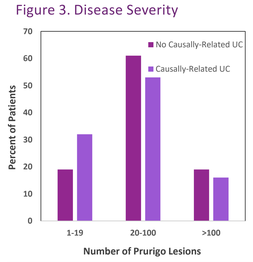


Figure 3. Disease Severity



Disease Severity was similar regardless of absence or presence of UCs

- Among patients in the group with causally-related UC and the group with no causally-related UC with available data, the number of prurigo lesions in the representative area was 10.4 (9.3) and 13.7 (11.2), respectively.
- Among those in the PN + UC group, 32% had an estimated 1-19 prurigo lesions, 53% had between 20-100 prurigo lesions, and 16% had >100 prurigo lesions
- In the PN + no UC group, 19% had an estimated 1-19 prurigo lesions, 61% had between 20-100 prurigo lesions, and 19% had >100 prurigo lesions.

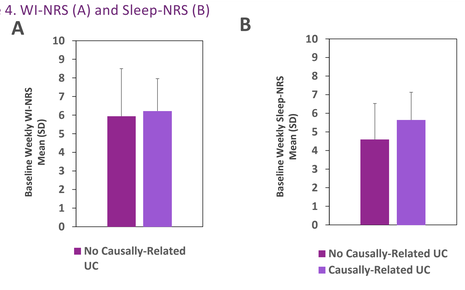
Pruritus similar with or without a Causally-Related Underlying Condition

- Consistently, 82% of patients, regardless of underlying conditions, described their pruritus as moderate to unbearable (5-D pruritus scale)

Pruritus intensity and sleep impairment were similar regardless of the absence or presence of causally-related UCs

- In the group with causally-related UC and the group with no causally-related UC baseline weekly average of daily eDiary worst-itch NRS was 5.94 (2.56) and 6.22 (1.74), respectively
- In the group with causally-related UC and the group with no causally-related UC weekly average of daily sleep quality NRS was 4.59 (1.94) and 5.64 (1.49), respectively.

Figure 4. WI-NRS (A) and Sleep-NRS (B)



IHC IL-31 Expression similar with or without a Causally-Related Underlying Condition

- IL-31-expressing mononuclear cells were present in 89% of lesional biopsies (immunohistochemistry) in PN with or without an UC reflecting the similarities in worst itch NRS scores in these 2 groups

IL-31 Expression increases with WI-NRS score regardless of presence or absence of Underlying Condition*

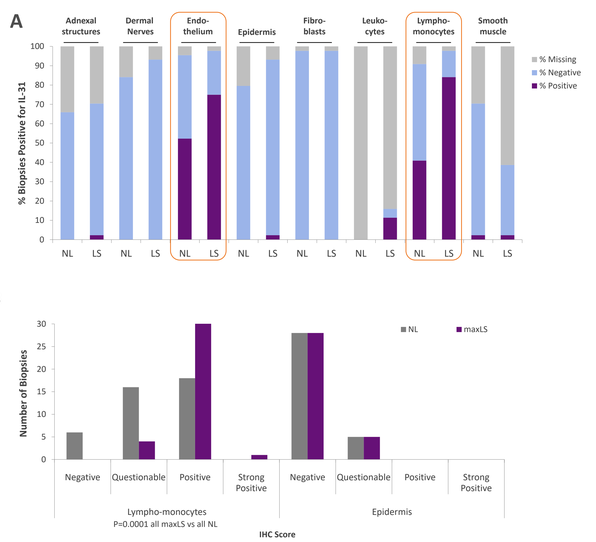
- IL-31, IL-31Rα, OSM, and OSMRβ expression in mononuclear cells was upregulated in lesional biopsies versus non-lesional biopsies (p≤0.001)

*Data previously presented/ SID 2019

IL-31 is Upregulated in Lesional vs non-Lesional PN skin

- Endothelial cells and lympho-monocytes were identified as primary sources of IL-31 production in PN biopsies (Figure 5A)
- Lympho-monocytes from LS PN biopsies expressed higher levels of IL-31 compared with lympho-monocytes from NL PN samples (P=0.0001; Figure 5B)

Figure 5. IL-31 Immunohistochemistry

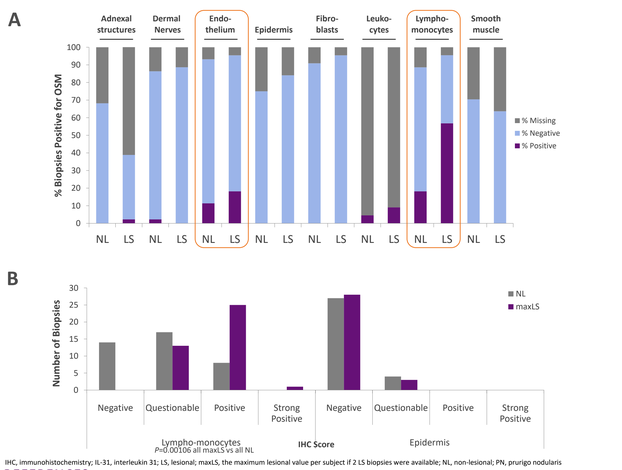


IHC, immunohistochemistry;
IL-31, interleukin 31; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; PN, prurigo nodularis

OSM is Upregulated in Lesional vs Non-Lesional PN Skin

- Endothelial cells and lympho-monocytes were identified as primary sources of OSM production in PN biopsies (Figure 6A)
- Lympho-monocytes from LS PN biopsies expressed higher levels of OSM compared with lympho-monocytes from NL PN samples (P=0.00106; Figure 6B)

Figure 6. OSM Immunohistochemistry



IHC, immunohistochemistry;
IL-31, interleukin 31; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; PN, prurigo nodularis

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DISCLOSURES

S Staender: PI for Menlo, Dermasense, Trevi, Galderma, Kiniksa and Novartis, advisory board member and consultant for Beiersdorf, Galderma, Celgene, Menlo, Nerre, Novartis, Pfizer, Sanofi, Sienna, Trevi; S Ekanayake-Bohlig: PI for Menlo, Galderma, Kiniksa, Bioskin, Innovaderm, Leo, Glennmarck, Janssen, Pfizer, Sanofi and Novartis; E Weisshaar: PI for Menlo, Trevi, Kiniksa, and advisory board member for Menlo and Trevi; G Yosipovitch: advisory board member and consultant for Kiniksa, Trevi, Sanofi Regeneron, Menlo, Eli Lilly, Novartis, Bayer, Cerrave, AbbVie, Pfizer, and grant support from Kiniksa, Menlo, Pfizer and Leo; M Mentz: speaker and/or consultant for argenx, Beiersdorf, Celgene, Galderma, Menlo, Nerre, Novartis, Roche, Sanofi, Sienna; J Silverberg: advisory board member or consultant for Abbvie, Anaptysbio, Arena, Asana, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Glenmarck, Kiniksa, Leo, Menlo, Novartis, Pfizer, Regeneron-Sanofi, Speaker for Regeneron-Sanofi, Grants from GlaxoSmithKline and Galderma; Z Mikhak: former Kiniksa employee; JF Paolini, J Pirrello, R Gandhi: Kiniksa employees; This study was sponsored by Kiniksa Pharmaceuticals Ltd. Medical writing assistance was provided by Emily Plummer, PhD, an employee of Kiniksa Pharmaceuticals Corp.

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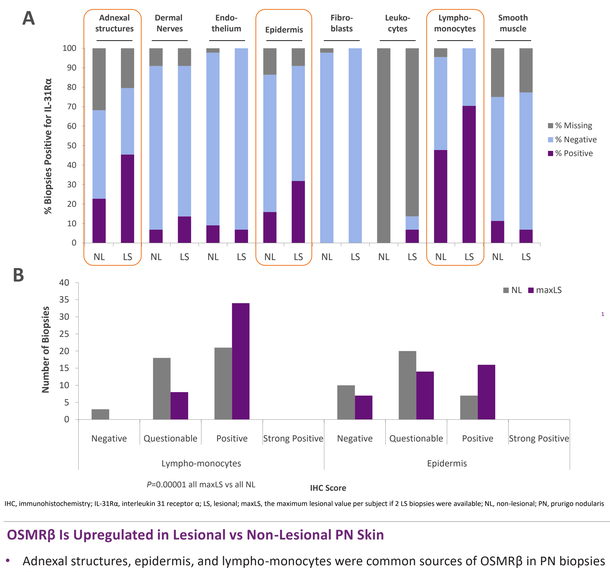
IL-31Rα Is Upregulated in Lesional vs Non-Lesional PN Skin

- Adnexal structures, epidermis, and lympho-monocytes were common sources of IL-31Rα in PN biopsies (Figure 7A)
- Lympho-monocytes from LS PN biopsies expressed higher levels of IL-31Rα compared with lympho-monocytes from NL PN samples (P=0.00001; Figure 7B)

Figure 7. IL-31Rα Immunohistochemistry

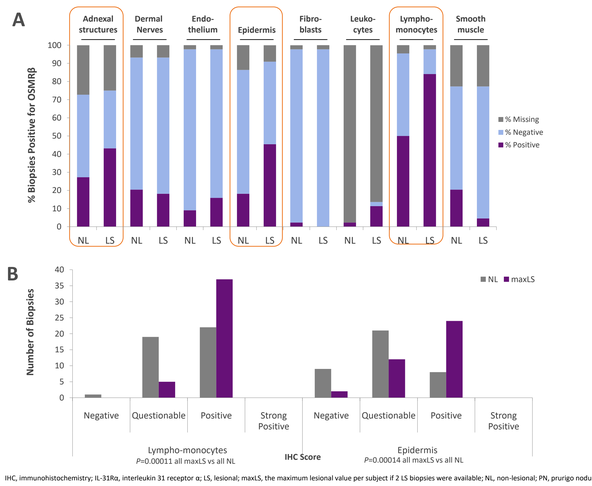


IHC, immunohistochemistry; IL-31Rα, interleukin 31 receptor α; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; PN, prurigo nodularis

OSMRβ Is Upregulated in Lesional vs Non-Lesional PN Skin

- Adnexal structures, epidermis, and lympho-monocytes were common sources of OSMRβ in PN biopsies (Figure 8A)
- Lympho-monocytes and epidermal cells from LS biopsies showed significantly higher expression levels of OSMRβ than lympho-monocytes and epidermal cells from NL biopsies (P=0.00011 and P=0.00014, respectively; Figure 8B)

Figure 8. OSMRβ Immunohistochemistry



IHC, immunohistochemistry; IL-31Rα, interleukin 31 receptor α; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; PN, prurigo nodularis

CONCLUSIONS

- Prurigo nodularis is a distinct, highly pruritic chronic skin disease that is not defined by its comorbid conditions.
- Disease severity is similar regardless of absence or presence of underlying conditions
- Pruritus intensity and sleep impairment appear not to correlate with underlying condition
- IL-31 expression is related to pruritus intensity
- The OSMRβ axis is upregulated in lesional versus non-lesional skin

The OSMRβ axis (IL-31, OSM, IL-31Rα, and OSMRβ) may play a role in the pathogenesis of PN given its prevalent expression in PN lesional skin and represents an attractive target for further study of pharmacological intervention in PN