Treatment of Recalcitrant Prurigo Nodularis with Dupilumab

Matthew T. Reynolds, MPAS, PA-C¹, Scott M. Dinehart, MD¹, Katlyn R. Anderson, MPAS, PA-C¹, Joe Gorelick, FNP-C²

¹Arkansas Dermatology, Little Rock, AR
²California Skin Institute, San Jose - Los Gatos, CA

ABSTRACT

Objectives: Prurigo nodularis (PN) is a disease of aberrant and recalcitrant itching which is difficult to effectively manage. There are no current FDA-approved therapies for PN. The current topical and systemic medications used for this condition provide less than optimal efficacy for the majority of patients with this condition and often have unacceptable side effects. We report 4 patients who were effectively treated with dupilumab (Dupixent) for the treatment of recalcitrant PN.

Methods: Four patients were treated successfully with dupilumab, a systemic biologic agent that is not immunosuppressive (Dupixent; Sanofi-Regeneron). Patients were treated with dupilumab monotherapy, without the use of other systemic immunosuppressing agents. The peak pruritus numerical rating scale (NRSi) was used to evaluate patients at weeks 0 and 4.

Results: Dupilumab therapy results in a dramatic reduction in NRSi scores by week 4 and that result continues throughout the duration of therapy. This reduction in itch is seen with continuous therapy.

Conclusion: Dupilumab therapy appears effective in reducing the overall itch severity in patients with PN. The usage of dupilumab as a monotherapy shows promise in the treatment of PN. The therapeutic response to dupilumab seen in PN suggests that the pathogenesis of PN may overlap with that of atopic dermatitis.

INTRODUCTION

Prurigo nodularis (PN) is a condition characterized by aberrant and recalcitrant itching. Patients scratch and pick at their pruritic skin which results in nodules that preferentially occur on the extensor aspects of the extremities and spare difficult to reach areas, like the upper-middle back. Treatment with various topical and systemic therapies is often ineffective. Many of the aggressive systemic therapies are also ineffective and associated with serious adverse events. We report four patients with recalcitrant PN who were treated successfully with dupilumab (Dupixent) (Table 1). All patients were treated with a standardized dose of dupilumab 600mg SC on day 1, then 300mg SC every other week thereafter. Itch scores at weeks 0,
4, and current were calculated according to the Pruritis Numerical Rating Scale (NRSi).

## CASES

**Case 1**
A 65-year-old woman with a five-year history of PN had an NRSi score of 10/10 prior to treatment with dupilumab. Previous therapies included pimecrolimus, clobetasol, prednisone, cetirizine, and loratadine. NRSi scores at weeks 0, 4, and current were as follows: 10, 2 and 0, respectively, for a total treatment length of 14 months. Currently, she is on dupilumab 300mg SC every other week and clobetasol ointment intermittently.

**Case 2**
A 17-year-old woman with a 15-year history of PN and NRSi score of 10/10 prior to starting dupilumab therapy. Previous therapies included topical clobetasol, IL Kenalog, hydroxyzine, Unna boot wraps, Bactrim DS, and prednisone. NRSi scores at weeks 0, 4, and current were as follows: 10, 2, and 1 for a total treatment length of 11 months. Currently, crisaborole and hydrocortisone lotion are used with dupilumab.

**Case 3**
A 46-year-old male with PN for six years and a baseline NRSi score of 10/10 was treated with dupilumab. Previous therapies: clobetasol, IM/IL Kenalog, prednisone, and pimecrolimus. After 13 months of therapy, the patient’s NRSi scores have reduced from 10 at week 0, 0 at week 4, with a current NRSi score of 0. He has been using clobetasol ointment intermittently in conjunction with his dupilumab injections.

**Case 4**
A 71-year-old woman with PN for > 4 years recorded a baseline NRSi score of 10/10. (Figure 1). Previous treatments include topical corticosteroids, IL Kenalog, pimecrolimus, crisaborole, doxycycline, methotrexate, and gabapentin. The patient’s NRSi scores have trended downward while on dupilumab from a score of 10 at week 0 to a score of 3 at week 4, respectively. Currently, her NRSi score is 1 at 16 months of therapy. She has been using Calamine lotion, Sarna lotion, and ice packs concomitantly with dupilumab therapy.

## DISCUSSION

Known risk factors for PN development include chronic atopic dermatitis, psychiatric factors, and underlying systemic disorders such as malignancies, renal failure, liver failure, and HIV infection. Currently, PN is categorized as a neurodermatitis despite having a pathogenesis that remains mostly unknown. Of note, interleukin (IL)-4 and 31 are upregulated in the lesional skin of PN patients. Additionally, atopic dermatitis (AD), a T-helper (Th) 2 cell-mediated disease, demonstrates increased expression of IL-4, 13, and the IL-31 receptor α-chain (IL-31RA). To date, numerous therapies are used to treat PN. Phototherapy with ultraviolet light (UV), psoralen plus ultraviolet A light (PUVA), ultraviolet A (UVA) light alone, and ultraviolet B light (UVB) alone as well as gabapentin reportedly have anecdotal efficacy. More aggressive immunomodulatory agents are often utilized: oral glucocorticoids, thalidomide, methotrexate (MTX), and cyclosporine, however, these therapies are often fraught with potentially detrimental side effects.

Recently, reports of PN patients treated with alternative non-FDA indicated agents, namely dupilumab (Dupixent) have gained attention. A case series of three patients with generalized PN were treated with standard
Table 1. Four patients with PN treated with dupilumab.

| Age | Disease Duration | Previous Therapies | Pathology Results | Concomitant Therapies | NRSi Score | Length of dupilumab Treatment |
|-----|------------------|--------------------|-------------------|-----------------------|------------|-------------------------------|
| 46  | 6 years          | Topical steroids, IM/IL Kenalog, Prednisone, pimecrolimus | LSC                | Clobetasol ointment   | Week 0: 10 | 13 months                     |
|     |                  |                    |                   |                       | Week 4: 0  |                               |
|     |                  |                    |                   |                       | Current: 0 |                               |
| 17  | 15 years         | Topical steroids, IL Kenalog, Hydroxyzine, Prednisone | 2013: Prurigo Nodularis 2018: Spongiotic Dermatitis | TAC, crisaborole | Week 0: 10 | 11 months                     |
|     |                  |                    |                   |                       | Week 4: 3  |                               |
|     |                  |                    |                   |                       | Current: 1 |                               |
| 65  | 5 years          | Pimecrolimus, topical steroids, prednisone, cetirizine, loratadine | Spongiotic and Psoriasiform Dermatitis | Patch testing: + MDBGN + Irritant: - Balsam of Peru - Ses. Lactone mix - Propylene Glycol | Clobetasol ointment | Week 0: 10 | 14 months                     |
|     |                  |                    |                   |                       | Week 4: 2  |                               |
|     |                  |                    |                   |                       | Current: 0 |                               |
| 71  | 4 years          | Topical steroids, IL Kenalog, pimecrolimus, crisaborole, Doxycycline, Methotrexate, Gabapentin | Prurigo Nodularis Shave biopsy: SCC (arising from PN areas) | Calamine, Sarna, Cold packs | Week 0: 10 | 16 months                     |
|     |                  |                    |                   |                       | Week 4: 3  |                               |
|     |                  |                    |                   |                       | Current: 1 |                               |

Figure 1. Patient 4 before dupilumab initiation (A) and at 3 months (B).
atopic dermatitis dosing (initially 600 mg, then 300 mg every two weeks). Patients were treated with concomitant systemic and topical therapies along with dupilumab. Overall itching was rated on a scale of 0 to 10 per the Pruritis Numerical Scale (NRSi). The average disease duration for these patients was 8.6 years. Two patients were on concomitant thalidomide and cyclosporine in addition to dupilumab therapy. Pruritis scores were measured on weeks 0, 4, 8, and 12, with results seen as early as week 4. By week 12, all participants remained on dupilumab with an average pruritis NRSi score of 1.8

Mollanazar et al. also described four patients treated with dupilumab for PN. All patients had a trial period of 15 mg of Mirtazapine, super-potent topical steroids, and a calcineurin inhibitor ointment before treatment with dupilumab. Pruritis was also measured according to the NRSi scale. The average NRSi score was 8.75 at week 0 and all patients ultimately reached an NRS itch score of 0 by the end of 8 weeks. Interestingly, three patients reported an NRSi score of 0 by week 4.9

We describe four patients with recalcitrant PN treated successfully with a dupilumab (Dupixent). Our patients had all received intensive topical and systemic treatments, which were mostly ineffective prior to initiation with dupilumab. In contrast to other cases reported, our patients were treated with a single systemic agent, dupilumab. Our patients used a variety of topical medications as adjunctive therapy. It appears that dupilumab can be effective monotherapy in patients with PN.

Dupilumab, a fully-humanized monoclonal IgG antibody that blocks the receptor site on Type 1 and Type 2 receptors for interleukin-4 alpha, blocks both the IL-4 and IL-13 signaling pathways. Activation of the T_{H2} pathway has often been thought to play a role in the development of PN lesions.10 Since dupilumab effectively blocks several key components of this pathway, there may be a possible, previously undescribed, inflammatory process in PN, similar to AD that warrants further investigation. In our subset of patients, patch testing was performed to reduce the potential of multi-causality for the development of PN. Previously, Boonstra et al., described patients with atopic dermatitis whom appear to have a higher rate of contact allergen sensitization. Although contact dermatitis is primarily mediated by the T_{H1} pathway, there has been evidence to suggest the allergens can induce T_{H2} cell-mediated signaling pathways.11

Conflict of Interest Disclosures: Reynolds – Consultant Sanofi/Regeneron, Lilly Pharmaceuticals, AbbVie, Novartis, Castle Biosciences, SUN, Primus; Speaker Sanofi/Regeneron, Novartis Dinehart – Speaker Regeneron; Consultant and Speaker, Genentech Gorelick – Consultant Sanofi/Regeneron; Consultant and Speaker Dermira; Consultant and Speaker Lilly Pharmaceuticals; Speaker Pfizer Anderson – No conflicts of interest

Funding: None

Corresponding Author: Matthew T. Reynolds, PA-C Arkansas Dermatology 4261 Stockton Drive, Suite 200 North Little Rock, AR 72117 Email: mreynolds@arkansasdermatology.com

References:
1. Stander S, Stumpf A, Osada N, Wilp S, Chatzigorgeakidis E, Pfleiderer B. Gender differences in chronic pruritus: women present different morbidity, more scratch lesions and higher burden. Br J Dermatol. 2013;168:1273-1280.
2. Winhoven SM, Gawkrodger DJ. Nodular prurigo: metabolic diseases are a common association. Clin Exp Dermatol. 2007; 32:224-225.
3. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2006;117:411-417.
4. Park K, Mori T, Nakamura M, Tokura Y. Increased expression of mRNAs for IL-4, IL-17, IL-22 and IL-31 in skin lesions of subacute and chronic forms of prurigo. Eur J Dermatol. 2011; 21:135-136.
5. Nakashima C, Otsuka A, Kabashima K. Interleukin-31 and interleukin-31 receptor: New therapeutic targets for atopic dermatitis. Exp Dermatol. 2018 Apr;27(4):327-331.
6. Bruni E, Caccialanza M, Piccinno R. Phototherapy of generalized prurigo nodularis. Clin Exp Dermatol. 2009;35:549-550.
7. Gencoglan G, Inanir I, Gunduz K. Therapeutic hotline: treatment of prurigo nodularis and lichen simplex chronicus with gabapentin. Dermatol Ther. 2010;23:194-198.
8. Beck, K., Yang, E., Sekhon, S., Bhutani, T., Liao, W. Dupilumab treatment for generalized prurigo nodularis. *JAMA Dermatology*. 2019; 155:118-120.
9. Mollanazar, N., Elgash, M., Weaver, L., Valdes-Rodriquez, R., Hsu, S. Reduced itch associated with dupilumab treatment in 4 patients with Prurigo Nodularis. *JAMA Dermatology*. 2019; 155:121-122.
10. Beck, LA., et.al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med*. 2014; 372(2):130-139.
11. Boonstra M, Rustemeyer T, Middelkamp-Hup MA. Both children and adult patients with difficult-to-treat atopic dermatitis have high prevalences of concomitant allergic contact dermatitis and are frequently polysensitized. *J Eur Acad Dermatol Venereol*. 2018 Sep;32(9):1554-1561.