

BRIEF ARTICLES

Treatment of Recalcitrant Prurigo Nodularis with Dupilumab

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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,

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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.^{1,2} 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.^{3,4} 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).⁵ 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.^{6,7} 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 duplimab Treatment
46	6 years	Topical steroids, IM/IL Kenalog, Prednisone, pimecrolimus	LSC	Clobetasol ointment	Week 0: 10 Week 4: 0 Current: 0	13 months
17	15 years	Topical steroids, IL Kenalog, Hydroxyzine, Prednisone	2013: Prurigo Nodularis 2018: Spongiotic Dermatitis	TAC, crisaborole	Week 0: 10 Week 4: 3 Current: 1	11 months
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 Week 4: 2 Current: 0	14 months
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 Week 4: 3 Current: 1	16 months

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 Pruritus 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. Pruritus 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 pruritus 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. Pruritus 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
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