Dupilumab as promising treatment for prurigo nodularis: current evidences

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ABSTRACT

Prurigo nodularis (PN) is a debilitating chronic disease characterized by intense itching and excoriated hyperkeratotic nodules distributed on the trunk and extremities, especially the extensor surfaces. The pathophysiology includes complex and not yet well-understood mechanisms involving inflammation and dysregulation of the nervous system. Currently, there are no approved therapies by the Food and Drug Administration (FDA) and the few treatment approaches for this condition are often ineffective and related to severe side effects. An emerging therapeutic option is dupilumab, a monoclonal antibody for adults and adolescents with moderate-to-severe atopic dermatitis, that inhibits interleukin-4 receptor alpha subunit (IL4-Rα) and the signaling pathways activated by interleukin (IL)-4 and IL-13. These cytokines seem to be involved in the development and perpetuation of PN and other type-2 inflammation diseases. Data on this topic are limited, but the emergent positive effects of this drug, reported in the literature and summarized in this review, suggest that it can be a safe and efficient therapy in PN.

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Introduction

Prurigo nodularis (PN) is an uncommon chronic pruritic skin disease characterized by hyperkeratotic, crusted or excoriated papules and nodules with hyperpigmented borders. The distribution of the lesions is usually symmetric and involves the trunk and the extensor surfaces of extremities; the predominant symptom is itching, but burning and stinging can also be present. Any age group can be affected, but the disease is most prevalent in adults-elderly (1).

The pathophysiology is not well understood, but the underlying mechanism seems to be a cutaneous neurogenic inflammation with the involvement of neuropeptides, T lymphocytes, mast cells, and eosinophilic granulocytes. The increase of IL-31 and other helper-2 T-cell (Th-2) cytokines, such as IL-4, and the dysregulation of several neuropeptides have all been implicated (2).

Furthermore, several inflammatory dermatoses can be connected with PN, with a predominance of atopic dermatitis, approximately half of all cases of PN has an atopic disposition with an increased number of allergic comorbidities (1).

The diagnosis of PN is established through a positive history of chronic, severe pruritus and the clinical finding of characteristic skin lesions; in case of doubts, a skin biopsy is performed to confirm the diagnosis.

There are few strategies to treat PN and often with unsatisfactory results or severe side effects. It is a debilitating disease and the principal aim of therapies is a decrease of itch intensity, starting with emollients and topical therapies such as steroids, calcipotriol, and pimecrolimus. Thanks to its anti-inflammatory effects also phototherapy can be employed, in particular ultraviolet B (UVB) narrowband and psoralen with ultraviolet A (PUVA), nevertheless, most of the patients require adjunctive systemic treatments.

Multimodal medical treatment approaches have been tried, the group of gabapentinoids (gabapentin and pregabalin), and one of the antidepressants (for example paroxetine, duloxetine, and amitriptyline) are an option to treat the neural pathogenesis of itch transmission and give a beneficial effect. Immunosuppressants are commonly employed, in particular methotrexate and cyclosporine, but there are severe side effects to consider before starting treatment. Even opioid receptor antagonists have a neuromodulatory role and they can be used with an antipruritic effect.

New therapeutic options have been studied, but at this time there are no approved therapies for PN by the FDA. The neurokinin-1 receptor (NK1R) antagonists, aprepitant and serlopitant, failed to show efficacy in reducing pruritus in the clinical trials and nemolizumab, a humanized monoclonal antibody against IL-31 receptor A, has demonstrated encouraging results in decreasing pruritus and skin lesions in phase II clinical trial, but it has been associated with several adverse effects, including gastrointestinal and musculoskeletal symptoms (2).

Other promising targets in PN therapy are the IL-4 and IL-13, which are inhibited by dupilumab, a monoclonal antibody approved for the treatment of atopic dermatitis.

In this review, we report the relevant results, found in the literature, of 128 patients suffering from recalcitrant PN and treated with dupilumab. The drug has to demonstrate the efficacy of itch response in the 2 ongoing phase 3 clinical trials (NCT04183335 and NCT04202679) (3,4).

Material and methods

A search of PubMed, Science.gov databases, and ClinicalTrials.gov was performed for the period 2010–2020 using the terms: 'dupilumab' or 'interleukin-4 receptor inhibitor' in combination with 'prurigo' or 'prurigo nodularis.' Only articles in English were selected. Eligible articles were assessed according to the Oxford Center for Evidence-Based Medicine 2011 guidelines Review articles, meta-analyses, observational studies, case reports, survey snapshot studies, letters to the editor, and comments to the letters were all included. Other potentially relevant articles were identified by manually checking the references of the included literature.

The last research was run in January 2021 with 128 patients from a total of 21 articles published in the literature, all included in this review.

Dupilumab mechanisms of actions

Allergic diseases, including atopic dermatitis, are characterized by Th-2 immune response, which is driven by specific cytokines such as IL-4, IL-5, IL-9, and IL-13 (5). Dupilumab is a fully human monoclonal antibody of immunoglobulin G-4 (IgG4) class, that targets the alpha chain of the interleukin-4 receptor (IL4-Rα). IL4-Rα is a subunit shared by the IL-4 receptor (named type I receptor) and IL-13 receptor (named type II receptor). Therefore, through competitive binding to IL4-Rα, dupilumab blocks the signal transduction cascade of both IL-4 and IL-13 (5,6).

The signaling pathways of type I and type II receptors, mediated by the Janus kinase/signal transducers and activators of transcription (JAK-STAT) phosphorylation, promote the activation of several genes involved in Th-2 inflammation, like those contributing to antibody switching and lymphocytes differentiation (5). Both receptors are expressed by different types of cells, like keratinocytes, bronchial epithelial cells, fibroblasts, smooth muscle cells, and cells of immunity (5). Therefore, IL-4 and IL-13 develop multiple actions, including activation of Th-2 and B lymphocytes, differentiation of dendritic cells, stimulation of IgE class-switching, and recruitment of eosinophils (7) and all these events are hindered by dupilumab.

Studies on skin gene expression in atopic dermatitis found that the administration of dupilumab downregulates markers of epidermal proliferation and inflammatory mediators, with a parallel upregulation of structural barrier proteins (6,7). This monoclonal antibody, blocking key-cytokines of Th2 response, contrasts the vicious cycle of inflammation and epidermal barrier damage typical of atopic dermatitis.

Recently, the FDA and the European Medicines Agency (EMA) approved dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents and for other type-2 inflammatory diseases: moderate to severe asthma in patients aged >12 years and chronic rhinosinusitis with nasal polyposis in adults. Clinical studies on dupilumab effectiveness and safety are ongoing in patients affected by other type-2 inflammatory conditions.

PN pathogenesis and the role of dupilumab

Even if the exact mechanisms underlying PN are not well understood, a pathogenic role of the Th2 pathway and the JAK/STAT activation have been suggested. Various epidermal biopsies of lesional skin in PN patients showed higher levels of nuclear expression of pSTAT6, a mediator of Th2 signaling, and an increased expression of IL-4 and IL-13 compared to controls (8). Sonkoly et al. showed, in PN lesions, important upregulation of IL-31, Th2 cytokines implicated in the pathogenesis of itching and inflammation (9). The presence of IL4-Rα, IL13-Rα1, and IL-31Rα in human dorsal root ganglia suggests that IL-4, IL-13, and IL-31 may directly activate sensory neurons.

The upregulation of type 2 cytokines and the high prevalence of atopic conditions in patients with PN indicate a potential role of dupilumab in patients suffering from this condition. However, it must be taken into account that there are also other mechanisms underlying this chronic itching. The skin of PN patients reveals a dermal hypersensitivity secondary to neuronal hyperplasia in the dermis, whereas there is an opposite situation in the epidermis with neuronal hypoplasia, that could be a consequence of recurrent scratching, but perhaps also the result of a subclinical cutaneous neuropathy (10,11).

The activated sensory neurons in the skin release substance P as an important modulator for the non-histaminergic itch, that binds neurokinin 1 receptor (NK1R) present on mast cells and releases pro-pruritic mediators (12). The complex interaction between nerve growth factor and the presence of eosinophils and mast cells leads to activation and sprouting of skin nerves and proliferation of keratinocytes.

The correct management of PN may remain a therapeutic challenge as long as its pathophysiology continues to be unclear.

Results

In recent years, relevant articles have been written related to the off-label use of dupilumab in patients with recalcitrant generalized PN. The majority of patients shared a history of the inadequately controlled disease and an atopic disposition. The disease was often refractory to multimodal treatment regimens (topical and systemic drugs, phototherapy) and the principal therapies used for PN prior to dupilumab were methotrexate, cyclosporine, and oral corticosteroids.

Characteristics of records are summarized in Table 1 and analyzed from 8 case reports (13–20), 8 case series (12,21–27), and 5 retrospective studies (28–32).

The dupilumab dose used for PN was the same dose approved for AD: 600 mg initial dose, then 300 mg every 2 weeks, furthermore, the patients could associate with other concomitant therapy. The only exception was the pediatric case of Fachler et al. in which a loading dose of 200 mg (8 mg/kg) was administered, followed by 100 mg (4 mg/kg) every 2 weeks (13).

The improvement onset varied, but overall it occurred within 6 months after the start of treatment, with a reduction in pruritus symptoms, a decrease in numbers and size of skin lesions, and an overall improvement of quality of life. According to the review of Husein-ElAhmed the clinical response to dupilumab starts later than patients with AD, the itch intensity decreases on average after 2 months of therapy and complete remission is rarely detected under 4 months of therapy (33). Furthermore, Tavecchio et al. observed that the treatment should not be discontinued until obtaining a satisfactory clinical response, because the reduction of skin lesions seems to be slower than in AD patients (28).

The literature search identified 128 patients treated with dupilumab and 5 of these showed no response (12–33).

Table 1. Dupilumab therapy in patients with prurigo nodularis.

No.	Ref.	Patients	Age	Atopy (Pts)	PN duration	DP duration (Pts)	Adjunctive therapies	Response	Pts with no response	DP adverse effects (Pts)
1	(12)	9 (M 3)	54.4 years (mean), range: 28–72 years	NA	NA	At least 8 weeks (6 Pts FUP 20 weeks or longer)	NA	Pruritus: CR in 6 Pts, SR in 3 Pts	0	No
2	(13)	1	9 years	No	3 years	1 y	No	Skin: SR within 2 weeks, almost CR after 3 months. Pruritus: SR	0	No
3	(14)	1	80 years	Adult-onset AD	1 years	15 months, discontinued for 1 month	PUVA (8 weeks), desloratadine (16 weeks)	Skin: SR within 10 weeks. Pruritus: slow and incomplete improvement	0	Herpes Zoster (trunk)
4	(15)	2	Pt 1: 53 years, Pt 2: 40 years	NA	Years (NA)	Pt 1: several weeks, Pt 2: several years	No	Skin and pruritus in Pt 1: SR Skin and pruritus in Pt 2: SR	0	Pt 1: new-onset alopecia?
5	(16)	1	63 years	No	27 years	10 months	No	Skin and pruritus: CR after 3 months	0	No
6	(17)	1	43 years	NA	3 years	2 months	No	Skin and pruritus: SR after 2 weeks	0	No
7	(18)	1	85 years	No	3 years	6 months	No	Skin: almost CR after 1 month, CR after 6 months. Pruritus: SR after 1 month, CR after 6 months	0	No
8	(19)	1	30 years	Resolved childhood AD, allergic conjunctivitis	10 years	8 months	NA	Skin: SR after 3 months, almost CR after 8 months. Pruritus: almost CR after 8 months	0	No
9	(20)	1 (M 1)	87 years	AD and atopic conditions	4 years	4 months	No	Skin: SR after 4 months. Pruritus: SR	0	No
10	(21)	3 (M 2)	61 years (mean)	NA	Pt 1: 15 years, Pt 2: 6 years, Pt 3: 5 years	3 months	Pt 1: GT, Pt 2: Fexofenadine hydrochloride, gabapentin, GT, pregabalin, thalidomide, Pt 3: CsA, dronabinol, gabapentin, GT, thalidomide	Skin in Pt1: almost CR after 3 months. Pruritus Pt 1: CR after 3 months. Skin and pruritus in Pt 2: SR after 3 months. Skin and pruritus in Pt 3: SR after 3 months	0	Pt 3: herpes labialis
11	(22)	3	Pt 1: 57 years, Pt 2: 48 years, Pt 3: 42 years	No	Pt 1: 3,5 years, Pt 2: 15 years, Pt 3: 21 years	Pt 1: 7 months, Pt2: 6 months, Pt3: 4 months	Pt 3: Naltrexone 4.5 + 1.5 mg daily	Skin and pruritus in Pt 1: CR, Skin and pruritus in Pt 2: SR, Skin and pruritus in Pt 3: SR	0	Pt 3: dry eyes
12	(23)	2 (M 2)	Pt1 60 years, Pt2 60 years	NA	NA	Pt 1: 9 months, Pt 2: 6 months	No	Skin in Pt1: SR. Pruritus in Pt 1: CR at 1-4-6-9 months. Skin in Pt1: SR. Pruritus in Pt2: CR at 2-3-6 months	0	No
13	(24)	3 (M 1)	Pt 1: 66 years, Pt 2: 65 years, Pt3: 65 years	Asthma and allergic rhinitis (1/3)	Pt 1: 2 years, Pt 2: NA, Pt 3: 3 years	Pt 1: 5 months Pt 1: 1 month Pt 1: 7 months	NA	Skin and pruritus in Pt 1: SR after 5 months, Skin and pruritus in Pt 2: SR after 1 month, Skin and pruritus in Pt 3: SR after 7 months	0	No
14	(25)	3 (M 2)	46 years (mean)	Atopic history (3/3)	3.1 years (mean)	6–9 months	No	Skin and pruritus in Pt 1: SR after 6 weeks.	0	No

(*continued*)

Table 1. Continued.

No.	Ref.	Patients	Age	Atopy (Pts)	PN duration	DP duration (Pts)	Adjunctive therapies	Response	Pts with no response	DP adverse effects (Pts)
								Pruritus in Pt 2: CR after 2 months. Pruritus in Pt 3: SR after 4 months		
15	(26)	4 (M 1)	40 years (mean)	Resolved childhood AD (1/4)	NA	3 months	NA	Pruritus: CR within 3 months	0	No
16	(27)	11 (M 7)	67 years (median) range: 62–78 years	Early-onset AD (8/11), adult-onset AD (2/11)	NA	4 weeks	NA	Skin and pruritus: SR after 4 weeks	0	No
17	(28)	18 (NA)	NA	Early-onset AD (5/18), adult-onset AD (13/18)	NA	52 weeks	NA	Skin and pruritus: SR at 4-16-52 weeks	NA	NA
18	(29)	27 (M 11)	52 years (mean), range: 23–83 years	AD o AD history (13/27), atopic diseases (5/27)	13.7 years (mean)	At least 16 weeks (23/27), FUP at 36 weeks (10/27)	NA	Skin in 23 Pts: SR after 16 weeks. Skin in 3 Pts: CR after 36 weeks. Pruritus in 23 Pts: SR after 16 weeks. Pruritus in 10 Pts: almost CR after 36 weeks	4 (after 4 weeks of therapy)	Conjunctivitis (8/27), hepatotoxicity due to increased dosage of antidepressants (1/27)
19	(30)	16 (M 7)	56 years (median)	AD (7/16), asthma (5/16), allergic conjunctivitis (4/16), allergic rhinitis (5/16)	6 years (median)	At least 3 months, FUP at 6 months (12/16), FUP at 12 months (6/16)	NA	Skin at 3 months: CR in 3 Pts, PR in 12 Pts, NR in 1 Pt. Pruritus at 3 months: CR in 5 Pts, PR in 9 Pts, NR in 2 Pts	3 (after 3 months of therapy)	Mild conjunctivitis (2/16), Mild worsening of celiac disease (1/16), eosinophilia (1/16)
20	(31)	11 (M 6)	51 years (mean), range: 19–88 years	AD (11/11)	NA	4 months	NA	Skin: CR/almost CR in 5 Pts after 4 months, SR in 6 Pts. Pruritus: SR after 1 month	0	Transitory psoriasiform dermatitis after first injection of dupilumab (1/11)
21	(32)	9 (M 4)	50.1 years (mean), range: 31–63 years	AD and $\geq$ 1 atopic conditions (9/9)	1.4 years (mean)	16-weeks	No	Skin and pruritus: SR after 16 weeks	0	No

Abbreviations. Ref.: reference; Pt: patient; Pts: patients; PN: prurigo nodularis; DP: dupilumab; M: male; NA: not available; FUP: follow-up; SR: significant response; CR: complete response; AD: atopic dermatitis; CsA: cyclosporine; GT: Goeckerman therapy; PR: partial response; NR: no response.

Chiricozzi et al. reported that 4 of 27 patients interrupted therapy for lack of efficacy or worsening of PN after 4 weeks of therapy (29) and in the French multicentre adult cohort study 1 of 16 adult patients did not have a response at three months (30).

The drug was generally well-tolerated and no serious treatment adverse events were reported. Beck et al. described one patient with Herpes labialis (week 9) resolved after treatment with acyclovir (21), in the paper of Kovács et al. the patient developed Herpes Zoster after 5 months of treatment, therefore the physicians started intravenous antiviral therapy and stopped dupilumab for 1 month (14), Holm et al. recorded 1 patient with dry eyes, easily resolved with lubricating eye drops (22). In the French multicentre study, 2 patients suffered from mild conjunctivitis, 1 patient had a slight worsening of celiac disease and 1 showed eosinophilia that did not require treatment discontinuation (30). In the retrospective multicentre Italian study with a large number of patients, 27 adults, treated with dupilumab for at least 16 weeks, the emerging side effects were mild conjunctivitis, within the first week, resolved with topical therapy and a patient, suffering from depression, showed episodes of hepatotoxicity due to increased dosage of antidepressants, therefore dupilumab therapy was interrupted and restarted after 8-week withdrawal (29). As previously described by Fowler et al. for AD, a case of transitory psoriasiform dermatitis after the first injection of dupilumab was also detected in a PN patient (31). Furthermore, in one case report, the new onset of alopecia in a woman treated with dupilumab was not felt to be drug-related, but the patient decided, however, to stop the treatment (15). One patient with PN and chronic heart failure were treated with dupilumab; the brilliant response after 10 months-follow-up may highlight the safety and the efficacy of the drug even in this type of patient with chronic heart failure, which is usually excluded from clinical trials (16).

Moreover, PN is very frequent in HIV-positive patients, but the effects of dupilumab in these patients are not well known. Mollanazar et al. decided to treat a severe type of PN in 2 HIV-positive patients with dupilumab, obtaining relief from itching and a significant reduction of skin lesions. These data may suggest that dupilumab can be a valid and safe option even in this type of patients, but further studies are required (23).

Phase 3 clinical trials of dupilumab therapy in PN

Currently, there are no FDA-approved therapies for PN, but there could be an important change with the results of the 2 studies (phase 3) evaluating dupilumab response in patients (18–80 years of age) with PN, inadequately controlled on topical therapies or when there are contraindications for these therapies (3,4).

Both are parallel multicentered, multinational, randomized double-blinded, placebo-controlled studies and are currently recruiting an estimated number of 150 participants each. The duration of both studies includes 2–4 weeks of screening time, 24 weeks of the treatment session, and 12 weeks of post-treatment period.

In the experimental arm, dupilumab is injected and can be associated with moisturizers and if applicable low to medium potent topical corticosteroids or topical calcineurin inhibitors.

The final data for the primary outcome measure have not yet been released, they will be provided in July–August 2021.

Discussion

Prurigo nodularis is a chronic skin disease that negatively affects the quality of life. The pathogenesis is still unknown, many mechanisms play a role in the development of skin lesions and symptoms.

A large portion of patients is resistant to available therapy and there are few therapeutic options to control the disease, often with important side effects.

Dupilumab, a new monoclonal antibody inhibiting the pathway of both IL-4 and IL-13, has shown exciting results in the treatment of AD and other type-2 inflammatory diseases.

Even if the exact mechanisms by which this drug may help PN patients is not well understood, the hypotheses include the inhibition of Th2 pathway and the interruption of neuronal interactions underlying chronic itch. IL-4 and IL-13 represent the principal key to break the chronic itch-scratch cycle and allow the skin to heal.

The important reduction in itching and the excellent improvement in skin lesions reported in the literature suggest that dupilumab is a safe and efficient therapy for PN with or without atopic conditions.

The patients with PN refractory to multimodal treatment regimens received dupilumab dosing approved for AD, in most cases, there was a significant response within 6 months of therapy. The failure in few patients may be the result of neuropsychological elements and disease duration, in fact, there is evidence that the central nervous system can perceive chronic pruritus even if peripheral stimuli are not present (14).

This treatment was generally well-tolerated, the side effects were mild in severity and already seen in AD patients, in particular, dry eyes and conjunctivitis; therefore, the adverse-effect profile of dupilumab seem to be better than other off-label therapy.

Currently, there are no FDA-approved therapies for PN, but the 2 ongoing placebo-controlled randomized studies may confirm this alternative treatment for recalcitrant PN.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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