

## Safety and Effectiveness of Dupilumab in Prurigo Nodularis

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Prurigo nodularis (PN) is a chronic debilitating skin condition characterized by multiple, variably sized, firm, flesh to pink colored nodules and papules commonly located on the extensor surfaces of the limbs. The lesions are typically pruritic, severely affect quality of life, and can occur in people of any age group [1].

PN pathogenesis is largely unknown. Histologically, structural neural changes, represented by thickened nerves in the dermis and reduced innervation density in the epidermis, along with overexpression of substance P, have lent support to the hypothesis of a hyperstimulation of itch neural pathways. However, it is uncertain how the itch-scratch cycle plays a role and whether the lesions are present before the pruritus or the pruritus causes the lesions [2]. Nevertheless, an inhibitor of the substance P receptor, neurokinin 1 (NK-1), has been recently shown to quickly achieve clinically meaningful itch reduction, suggesting that the substance P/NK-1 pathway is an important target for treating chronic itch [3]. Conversely, all other medications tried thus far to alleviate symptoms of this intractable condition, such as immunosuppressants or drugs targeting nerve fibers, as well as phototherapy, have yielded inconsistent benefit [4]. Moreover, most of these treatments are empirical, as they have not been subjected to randomized controlled studies. Apart from substance P, interleukin (IL)-31, a T helper 2 (Th2) cytokine, has also been recently shown to be an important mediator of different chronic types of itch [5]. Indeed, evidence suggests that Th2 cytokines may play a major role in PN pathogenesis. Using antibodies against the signal transducers and activators of transcription (STAT) 1, 3, and 6, researchers have been able in fact to detect a Th2 signature in most patients with PN, as determined by the positive staining of the entire epidermis with anti-pSTAT 6, an

intracellular signaling molecule for such Th2 cytokines as IL-4 and IL-13 [6,7]. Thus, targeting the Th2 pathway may turn out to be a beneficial therapeutic strategy.

Dupilumab is a fully human monoclonal antibody targeting the  $\alpha$  chain of the IL-4 receptor, thereby blocking IL-4 and IL-13 biologic effects. Dupilumab is indicated for allergic asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyposis in Europe. However, because of its peculiar mechanism of action, it may also be theoretically beneficial for other Th2-mediated diseases [8]. A substantial proportion of PN patients are believed to harbor an atopic diathesis, as up to 50% of PN patients may present with overlapping features of atopic dermatitis [1]. This may hint at a role for dupilumab in PN treatment.

A 61-year old woman, suffering from generalized PN since age 34, was referred to our outpatient clinic for evaluation. She had already seen a number of doctors, been to several clinics, undergone skin biopsies (histology consistent with PN), and tried all of the proposed therapeutic options, with no appreciable benefit. PN lesions appeared one year after completing chemoradiotherapy for breast cancer, diagnosed at age 33. Quadrantectomy had also been performed. At age 53, because of dyspnea and fatigue, the patient underwent cardiologic evaluation which revealed a dilated left ventricle with an ejection fraction of 35%, along with mild mitral and aortic insufficiency. The final diagnosis was dilated cardiomyopathy, likely due to the previous oncologic treatments. At age 54, due to worsening dyspnea, the patient underwent coronary catheterization and angiography which did not disclose obstructive vascular lesions. The patient underwent cardioverter-defibrillator implantation and was discharged with a diagnosis of chronic heart failure due to nonischemic hypokinetic cardiomyopathy.

On physical examination, the patient had multiple erythematous, excoriated or lichenified, papules and nodules on the trunk and extremities (Figure 1 and online-only supplementary figure). Routine laboratory tests did not disclose abnormalities. Interestingly, the patient had high total IgE levels (2213 UI/ml, n.v.:  $\leq 100$ ) but no specific IgE to common allergens. Features of atopic dermatitis were not observed. The Dermatology Life Quality Index (DLQI) was 18, pruritus and sleep loss were 10/10 and 8/10, respectively, on a numerical rating scale (0-10). Consideration for dupilumab as a last resort treatment was made. Unlike

TNF- $\alpha$  inhibitors, which are contraindicated in patients with heart failure, there are no reported red flags for dupilumab in patients with heart disease; however, these patients are usually excluded from clinical trials, thus dupilumab effects on heart function are actually unknown. Eventually, upon consideration of possible risks and benefits, the patient agreed to start dupilumab, according to the schedule used in atopic dermatitis (600 mg followed by 300 mg every other week subcutaneously). Lesions improved very quickly (figure 1, right panel), and so did itch (4/10, 2/10, and 0/10 after one, two and three months of treatment, respectively) and night rest (sleep loss 4/10, 0/10, 0/10 after one, two and three months of treatment, respectively). DLQI was 2 at the 3-month evaluation. Five months after starting dupilumab, serum total IgE levels were basically unchanged, as only a slight reduction was observed (2101 UI/ml, n.v.:  $\leq 100$ ), as opposed to the dramatic response on skin lesions and subjective symptoms. At the latest follow-up, nearly ten months since starting dupilumab, with the patient still continuing the treatment with the monoclonal antibody, no signs and/or symptoms of worsening heart failure have emerged. Besides, the patient has not reported any other complaint among those listed in the package leaflet.

The brilliant response to dupilumab suggests a prominent pathogenic role for Th2-mediated immune responses in triggering the vicious itch-scratch cycle and the resulting structural neural changes. Noteworthy, despite quite high total IgE levels, dupilumab was nonetheless able to fully interfere with the underlying Th2 signature of the patient; this also raises the question as to whether baseline IgE levels may predict the extent of clinical response to dupilumab. Whatever the pathophysiologic mechanism, this case adds additional evidence on the well-known effectiveness of dupilumab in generalized PN [9,10] and, above all, underscores its safety even in such frail individuals as chronic heart failure patients. Thus, further exploration of dupilumab in PN patients is warranted, with larger numbers of patients and longer follow-up needed to confirm the effectiveness and safety of this biological approach.

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**Conflicts of interest**

The author has no conflict of interests to declare.

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**Figure.** Left panel: diffuse involvement of skin by PN lesions immediately before starting dupilumab treatment.

Right panel: complete resolution of skin lesions at the 3-month follow-up visit. Only depigmented lesions on intact skin are visible.



**pre-dupilumab**



**3-month follow-up during dupilumab treatment**