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].

The pathogenesis of PN 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 hyperstimulation of the neural pathways for itch. 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]. An inhibitor of the substance P receptor, neurokinin 1 (NK-1), was recently shown to quickly achieve clinically meaningful reduction of itch, suggesting that the substance P/NK-1 pathway is an important target in treatment of chronic itch [3]. Conversely, all other medications assayed thus far to alleviate symptoms of this intractable condition, such as immunosuppressants, drugs targeting nerve fibers, and phototherapy, have yielded inconsistent benefits [4]. Moreover, most of these treatments are empirical, as they have not been assessed in randomized controlled trials. Apart from substance P, interleukin (IL) 31, a type 2 helper T cell (T_H2) cytokine, was also recently shown to be an important mediator of various types of chronic itch [5]. Indeed, evidence suggests that T_H2 cytokines may play a major role in the pathogenesis of PN. Using antibodies against the signal transducer and activator of transcription (STAT) proteins 1, 3, and 6, researchers have detected a T_H2 signature in most patients with PN, as determined by positive staining of the entire epidermis with anti–pSTAT 6, an intracellular signaling molecule for T_H2 cytokines such as IL-4 and IL-13 [6,7]. Therefore, targeting the T_H2 pathway may prove to be a beneficial therapeutic strategy.

Dupilumab is a fully human monoclonal antibody targeting the α chain of the IL-4 receptor, thereby blocking the biologic effects of IL-4 and IL-13. 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 T_H2-mediated diseases [8]. A substantial proportion of PN patients are believed to have atopic diathesis, as up to 50% of PN patients may present with overlapping features of atopic dermatitis [1]. This observation may point to a role for dupilumab in treatment of PN.

A 61-year-old woman who had had 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. The PN lesions appeared 1 year after completion of chemoradiotherapy for breast cancer, which was diagnosed at age 33. Quadrantectomy was also performed. At age 53, because of dyspnea and fatigue, the patient underwent a 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 cancer treatments. A coronary angiogram performed at age 54 because of worsening dyspnea did not disclose obstructive vascular lesions. The patient underwent implantation of a cardioverter-defibrillator and was discharged with a diagnosis of chronic heart failure due to nonischemic hypokinetic cardiomyopathy.

Figure. A, Diffuse involvement of skin in the form of PN lesions immediately before initiation of treatment with dupilumab. B, Complete resolution of skin lesions at the 3-month follow-up visit. Only depigmented lesions on intact skin are visible.

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On physical examination, the patient had multiple erythematous, excoriated, and lichenified papules and nodules on the trunk and extremities (Figure and online-only supplementary figure). Routine laboratory tests did not disclose abnormalities. Interestingly, the patient had high total IgE levels (2213 IU/mL [reference value, ≤100]) but no specific IgE to common allergens. Features of atopic dermatitis were not observed. The Dermatology Life Quality Index (DLQI) was 18, and pruritus and sleep loss were 10/10 and 8/10, respectively, on a numerical rating scale (0-10). Dupilumab was considered a treatment of last resort. Unlike TNF-α inhibitors, which are contraindicated in patients with heart failure, there are no reported red flags for dupilumab in patients with heart disease; however, since these patients are usually excluded from clinical trials, the effects of dupilumab on heart function are actually unknown. Eventually, after 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). The lesions improved very quickly (Figure, right panel), as did itch (4/10, 2/10, and 0/10 after 1, 2, and 3 months of treatment, respectively) and night rest (sleep loss 4/10, 0/10, 0/10 after 1, 2, and 3 months of treatment, respectively). DLQI was 2 at the 3-month evaluation. Five months after starting dupilumab, serum total IgE levels remained mainly unchanged, with only a slight reduction (2101 IU/mL [reference value, ≤100]), as opposed to the dramatic response for skin lesions and subjective symptoms. At the latest follow-up visit, nearly 10 months after starting dupilumab, with the patient continuing the monoclonal antibody, no signs and/or symptoms of worsening heart failure have emerged. Besides, the patient has not reported any of the other complaints listed in the package leaflet.

The excellent response to dupilumab suggests a prominent pathogenic role for T_H2-mediated immune responses in triggering the vicious itch-scratch cycle and the resulting structural neural changes. It is noteworthy that despite quite high total IgE levels, dupilumab was able to fully interfere with the patient's underlying T_H2 signature; 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 patients with chronic heart failure. 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 declares that he has no conflicts of interest.

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SUPPLEMENTARY MATERIAL

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

Lower 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

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