



Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo

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Background: Chronic nodular prurigo (CNPG) is a multifactorial skin disease characterized by itchy papules and nodules, usually resistant to standard treatment and associated with markedly impaired quality of life.

Objective: To describe dupilumab effectiveness and tolerability in treating adult patients with CNPG refractory to both topical and systemic therapies.

Methods: Retrospective, multicenter study including adult patients affected by CNPG, who were treated with dupilumab for at least 16 weeks.

Results: Twenty-seven CNPG patients showed clinical improvement in terms of skin lesions, itch, sleeplessness, and quality of life. A consistent proportion of patients (24/27; 88.9%) had at least 16-week continuous treatment and achieved Investigator Global Assessment score 1 (11/24; 45.8%). An increased number of patients achieved at least a 2-grade reduction in Investigator Global Assessment score (19/24; 79.2%). Numeric rating scale values for itch and sleeplessness decreased from 8.9 to 2.7 and from 8.2 to 1.7, respectively ($P < .001$) after 16-week therapy. Ten patients achieved 36 weeks of continuous treatment while maintaining clinical efficacy.

Limitations: Major limitations included lack of validated assessment tools at the initial data collection, a limited cohort of treated patients, and a short-term observation period.

Conclusion: Dupilumab was proven effective in reducing itch and improving CNPG skin lesions. (J Am Acad Dermatol 2020;83:39-45.)

Key words: atopic dermatitis; dupilumab; itch; nodular prurigo.

INTRODUCTION

Chronic nodular prurigo (CNPG) is a subtype of chronic prurigo clinically characterized by severe

itching, inflamed excoriated papules, and nodules generalized or localized in the upper and lower extremities and buttocks.^{1,2} Prevalence and incidence

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Funding sources: None.

Conflicts of interest: Dr Chiricozzi served as speaker and advisory board member for Sanofi Genzyme, dupilumab manufacturer. Drs Maurelli, Gori, Argenziano, De Simone, Calabrese, Girolomoni, and Peris have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by Fondazione Policlinico Universitario Agostino Gemelli IRCCS—Università Cattolica del Sacro Cuore, Prot 24169/19-0040941/19; ID: 2605.

Accepted for publication March 18, 2020.

Reprints not available from the authors.

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Published online March 27, 2020.

0190-9622/\$36.00

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<https://doi.org/10.1016/j.jaad.2020.03.049>

are not defined, although CNPG is reported to occur more frequently in the elderly, in individuals aged between 51 and 65 years, and in blacks with atopic dermatitis compared with other racial groups.³⁻⁵

Although the pathogenic mechanism underlying CNPG is not fully understood, the disease is widely recognized as a skin reaction to continuous and

repeated rubbing or scratching caused by pruritus of multifactorial origin.²

Numerous diseases have been associated with CNPG, including pruriginous dermatoses (atopic dermatitis, bullous pemphigoid, scabies, T-cell lymphoma, dermatitis herpetiformis, lichen planus, psoriasis, asteatotic eczema, and both allergic and irritant contact dermatitis), chronic renal failure, liver and gastrointestinal disease (primary biliary cirrhosis and primary sclerosing cholangitis), cancers (lymphoma, bladder carcinoma, and gastric cancer), infections and infestations (HIV, hepatitis C virus, strongyloidiasis, and oxyuriasis), diabetes, chronic anemia, and psychiatric disorders such as depression, anxiety, and obsessive-compulsive disorder.^{1,3,6} Atopy is identified as one of the most relevant factors to be associated with CNPG because it occurs in approximately half of cases. CNPG has also been proposed as a clinical variant of atopic dermatitis, underscoring relevant similarities emerging from atopic dermatitis and CNPG.⁷ Indeed, several lines of evidence have suggested the potential role of Th2 immunity in the pathogenesis of CNPG, and its inhibition may result in clinically successful treatment of CNPG patients.⁸⁻¹⁰ The intense itch experienced by patients affected by CNPG is usually resistant to standard treatment and associated with markedly impaired quality of life.⁶ No therapy approved for the treatment of CNPG is currently available and off-label treatments are used, including topical corticosteroids, topical calcineurin inhibitors, topical capsaicin, phototherapy, and systemic agents (ie, cyclosporine, methotrexate, antidepressants, gabapentinoids, μ -opioid receptor antagonists, and neurokinin 1 receptor antagonists), notwithstanding inconsistent and often limited clinical benefit. When CNPG is correlated with other disorders such as infections and liver and renal diseases, specific treatments can more effectively alleviate it.^{1,11,12}

Dupilumab, a fully human monoclonal antibody inhibiting the signaling pathway of both interleukin

(IL) 4 and IL-13, has been recently approved for the treatment of moderate to severe atopic dermatitis,¹³ and its use has been reported in CNPG case series and case reports, showing beneficial effects on both skin manifestations and symptoms.¹⁴⁻²⁴

We performed a multicenter study to describe dupilumab effectiveness and tolerability in treating

adult patients with CNPG refractory to both topical and systemic therapies, during an observation period of 36 weeks.

PATIENTS AND METHODS

This retrospective, multicenter study included adult patients (≥ 18 years) affected by CNPG who were treated with dupilumab for at least 16 weeks during April 2018 to August 2019. The study population consisted of patients referred to dermatologic outpatient clinics of the

3 involved University centers: Catholic University of Rome, University of Verona, and University of Campania "Luigi Vanvitelli," Naples, Italy.

Diagnosis was based on the following criteria: chronic pruritus (≥ 6 weeks), history or signs of repeated scratching (eg, excoriations, scars), and localized or generalized presence of multiple pruriginous lesions (definition of pruriginous lesion: excoriated, scaling, or crusted papules, and nodules or plaques, often with a whitish or pink center and hyperpigmented border).²

For each patient, demographic and clinical data (ie, sex, age, height, weight, body mass index, waist circumference, personal and family history of CNPG, age at CNPG onset, anatomic site of skin lesions, disease duration, atopic manifestations, other comorbidities, previous and current treatments, and medications) were obtained from the database of each clinic. Patients were treated with subcutaneous injections of dupilumab at the labeled dose for atopic dermatitis, 600 mg at baseline followed by 300 mg every 2 weeks. Any adverse event, patient's decision, or unresponsiveness constituted cause for treatment interruption.

In cases not associated with atopic dermatitis, dupilumab was prescribed with the approved dose for atopic dermatitis. Visits were performed at baseline, week 4, week 16, and then every 20 weeks. At each visit, including baseline and follow-up visits, disease severity was assessed by (1) the Investigator

CAPSULE SUMMARY

- Case series and case reports have showed effectiveness of dupilumab in treating chronic nodular prurigo.
- This retrospective case series demonstrates efficacy of dupilumab in treating chronic nodular prurigo. Dupilumab's effect on skin lesions, itch, sleeplessness, and quality of life in chronic nodular prurigo suggests that the itch in chronic nodular prurigo is likely mediated by the T helper 2 pathway.

Abbreviations used:

CNPG:	chronic nodular prurigo
DLQI:	Dermatology Life Quality Index
IGA:	Investigator Global Assessment
IL:	interleukin
NRS:	numeric rating scale
SD:	standard deviation

Global Assessment (IGA) scale, as illustrated in Supplemental Fig 1 (Supplemental Figures available via Mendeley at <https://doi.org/10.17632/38h7p8kjp3.1>), classifying disease severity as no disease (0), very mild (1), mild (2), moderate (3), severe (4), and very severe (5); (2) a 0-to-10 numeric rating scale (NRS) for itch; (3) a 0-to-10 NRS for sleeplessness; and (4) the Dermatology Life Quality Index (DLQI). On a paper 0-to-10 visual scale, patients marked their score estimation for both itch and sleeplessness NRS.

Times and DLQI and NRS itch scores were established according to requirements of the regulatory Italian agency for drug prescription (Italian Agency for Drugs). We used the IGA and NRS for sleeplessness scores to implement the assessment of CNPG severity. Safety was evaluated by treatment-emergent adverse events, physical examinations, and laboratory monitoring. The study was approved by each local ethical committee and conducted in accordance with the Declaration of Helsinki guidelines.

Statistical analyses

Descriptive statistics were calculated for each demographic and clinical variable, using frequencies and percentage for categorical variables and mean \pm standard deviation (SD) for continuous ones. χ^2 Test or Fisher's exact test was used as appropriate for categorical variables. *t* Test or Mann-Whitney *U* test was used as appropriate for continuous variables. To verify any significant difference of clinical response between atopic dermatitis-related CNPG and atopic dermatitis-unrelated patient sub-cohorts, Fisher's exact test was used as appropriate for IGA score modifications, and Mann-Whitney *U* test as appropriate for DLQI, NRS for itch, and NRS for sleeplessness score modifications at weeks 4, 16, and 36. In all cases, $P < .05$ was considered statistically significant.

RESULTS

Twenty-seven white CNPG patients, 11 men and 16 women, treated with dupilumab were included in the study. Patients' demographic and clinical characteristics are illustrated in Table I. Mean age was

Table I. Baseline characteristic and demographics

Total patients	27
Men/women	11/16
Mean age (SD), y	52.0 (15.9)
Mean BMI (SD)	25.6 (3.4)
History of AD or AD manifestations	13/27
Family history of AD	8/27
Allergic rhinitis	14/27
Asthma	6/27
Allergic conjunctivitis	3/27
Diabetes	5/27
Hypertension	6/27
Hypothyroidism	2/27
Psychiatric disorders	8/27
Obesity	3/27
Mean age at CNPG onset, y	40.5 (16.3)
Mean CNPG duration, y	13.7 (13.6)
Mean baseline IgE serum levels, IU/mL	423.1
Patients with >1 previous systemic treatment	27/27
Patients with >2 previous systemic treatments	19/27

AD, Atopic dermatitis; BMI, body mass index; CNPG, chronic nodular prurigo; Ig, immunoglobulin; SD, standard deviation.

52.0 years (SD 15.9 years; minimum age 23 years; maximum age 83 years) and mean age of CNPG onset was 40.54 years (SD 16.3 years), with mean disease duration of 13.7 years (SD 13.6 years). Thirteen of 27 patients (48.1%) had a history of atopic dermatitis or concomitant atopic dermatitis manifestations, 5 had no atopic dermatitis but had other atopic manifestations (allergic rhinitis, asthma, and conjunctivitis), and 9 (33.3%) had no atopic manifestations.

All patients had been previously treated with at least 1 systemic treatment, and 13 of 27 failed at least 3 systemic treatments before dupilumab therapy. Cyclosporine and oral corticosteroids were the most commonly used therapies before dupilumab treatment (22/27 and 19/27, respectively). Other previously performed therapies included phototherapy (12/27), methotrexate (8/27), and azathioprine (7/27). Baseline disease severity, assessed by a 0-to-5 IGA score, was classified as IGA score 4 in 11 of 27 patients and IGA score 5 in 16 patients (Fig 1). Mean baseline values for the NRS for itch and sleeplessness were 8.9 (SD 1.0) and 8.2 (SD 2.0), respectively. All patients had both NRS itch and sleeplessness values greater than 7. The mean baseline DLQI score for quality of life was 21.0 (SD 4.0).

At week 4, clinical improvement was assessed by IGA and showed a reduced number of patients with CNPG scores of 5 (7) and 4 (2) (Fig 1). Fourteen of 27 patients (51.8%) achieved at least a 2-grade reduction in IGA score. Significant reduction of both itch and sleeplessness NRS values (from 8.9 to 6.3 and from

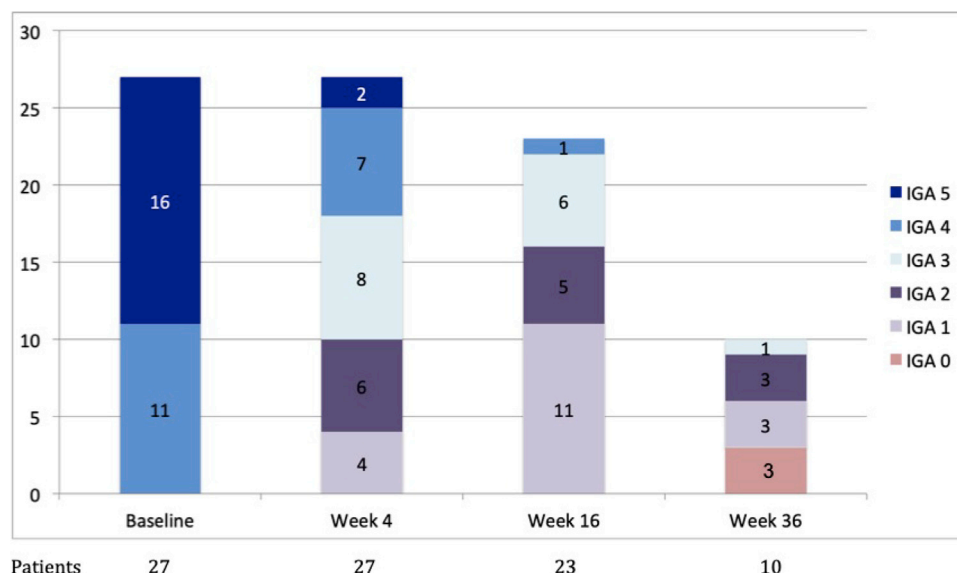


Fig 1. Disease severity assessed by the Investigator Global Assessment scale at different times. A progressively lower number of patients with Investigator Global Assessment score 4 or 5 were observed throughout the observation period. *IGA*, Investigator Global Assessment.

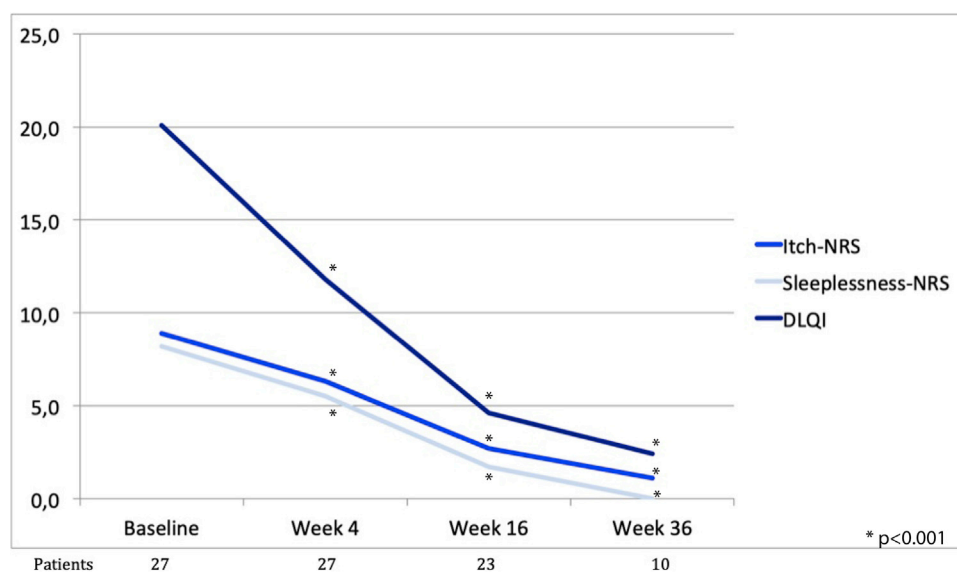


Fig 2. Improvement of both symptoms and patients' quality of life during dupilumab therapy. Reduction of the numeric rating scale score for itch and sleeplessness, and of the Dermatology Life Quality Index score, at weeks 4, 16, and 36. Score reductions for each tool were significant at all points compared with baseline values. Statistical analysis was performed with the Student *t* test. *DLQI*, Dermatology Life Quality Index; *NRS*, numeric rating scale.

8.2 to 5.5, respectively; $P < .001$) was obtained in the majority of patients and was associated with a DLQI score reduction (from 21.0 to 11.8; $P < .001$) (Fig 2). Four of 27 patients interrupted therapy for lack of efficacy or worsening of CNPG after 4 weeks of therapy.

A consistent proportion of patients (23/27; 85.2%) had at least 16-week continuous treatment and

achieved IGA score 1 (11/23; 47.8%) or 2 (5/23; 21.7%). An increased number of patients achieved at least a 2-grade reduction in IGA score (19/23; 82.6%). NRS values for itch and sleeplessness decreased from 8.9 to 2.7 and from 8.2 to 1.7, respectively ($P < .001$). Ten patients achieved 36 weeks of continuous treatment while maintaining clinical efficacy (Figs 1 and 2). Treatment response did not differ between

atopic dermatitis–related and –unrelated CNPG. We did not detect any meaningful difference in terms of itch amelioration, sleep improvement, and DLQI score reduction between atopic dermatitis–related CNPG (Supplemental Fig 2) and atopic dermatitis–unrelated patient subcohorts (Supplemental Fig 3). Dupilumab treatment response appeared to be faster in patients with atopic dermatitis–related CNPG (Supplemental Fig 2) compared with atopic dermatitis–unrelated CNPG in terms of IGA score reduction (Supplemental Fig 3). Along these lines, the same number of patients who dropped out (2 patients in each subcohort) was observed.

Overall, treatment-emergent adverse events consisted of 8 cases of mild conjunctivitis treated with tear substitutes and corticosteroid eyedrops (fluorometholone 0.1%), but none caused treatment interruption. Three of 8 patients had a history of conjunctivitis before dupilumab therapy, and 7 of them presented with rhinitis, 4 with asthma, and 5 with atopic dermatitis–associated CNPG. In 1 patient with CNPG associated with depression, who was under treatment with antidepressants, dupilumab therapy was discontinued after 16 weeks of treatment because of the occurrence of hepatotoxicity caused by an increased dosage of antidepressants. However, the patient was re-treated after 8-week withdrawal.

DISCUSSION

CNPG is a multifactorial skin disease characterized by chronic itch (lasting more than 6 weeks), history or signs of prolonged scratching behavior, and multiple localized or generalized nodular lesions that might be associated with 1 or more underlying conditions causing pruritus.^{1,2,6,7,25} This suggests that chronic pruritus induced by different causes leads to an itch-scratch cycle characterized by a neuronal sensitization with subsequent development of the typical nodular and excoriated skin lesions.^{6,7,25} In one survey of patients with CNPG, an association with dermatologic, neurologic, and mixed disorders was found in 87% of patients and included dermatologic (19%), systemic (7%), neurologic (2%), and mixed-origin (59%) diseases.⁷ In line with previous observations, our study showed that approximately 50% of patients (13/27) had a history of atopic dermatitis, whereas 5 patients had a family history of atopic dermatitis or concomitant atopic comorbidities, including asthma, conjunctivitis, and rhinitis. Cases with atopic dermatitis predisposition can be considered prurigo-like atopic dermatitis that is currently recognized as a clinical variant of atopic dermatitis.²⁶ Nevertheless, CNPG unrelated to atopic dermatitis may also benefit from dupilumab therapy because

pathogenic evidence linking CNPG to the Th2 pathway has been reported. Although CNPG pathogenesis is not fully understood, an emerging pathogenic role of the Th2 signaling has been suggested.⁸⁻¹⁰ Sonkoly et al⁹ showed significant upregulation of IL-31, one of the Th2-signature cytokines involved in the pathogenesis of pruritus and inflammation in CNPG lesions compared with healthy skin. Overexpression of another Th2-derived cytokine, namely, IL-4, was detected in CNPG lesional skin.⁸ Additionally, CNPG lesional skin showed an increased keratinocyte nuclear expression of phosphorylated signal transducer and activator of transcription 6, a key transcriptional factor mediating Th2 signaling.¹⁰ A murine model of chronic itch suggested the contribution of both IL-4 and IL-13 in stimulating itch-sensory neuronal pathways through IL-4R α and IL-13R α 1 receptor, and Janus kinase 1 signaling. The expression of receptors binding to Th2 cytokines in murine-sensitive neurons was confirmed in human dorsal root ganglia and direct activation of sensorial neurons by IL-4 and IL-13.²⁷

All the above-mentioned evidence supports the use of dupilumab in treating CNPG, whether associated with atopic dermatitis or not.^{16,24} In our study, no difference in response to treatment was detected in atopic dermatitis patients with CNPG compared with patients with atopic dermatitis–unrelated CNPG, representing approximately half of our study population (14/27). Itch amelioration, sleep improvement, and DLQI score reduction were similar between atopic dermatitis–related CNPG and atopic dermatitis–unrelated patient subcohorts, whereas in terms of IGA score reduction, dupilumab treatment response appeared to be faster in patients with atopic dermatitis–related CNPG compared with atopic dermatitis–unrelated CNPG. Nevertheless, the limited number of patients for each subcohort did not allow any further statistical analysis and this faster IGA score reduction in patients with atopic dermatitis–related CNPG was not consistent with the other findings. In addition, most patients (8/10) achieving 36 weeks of treatment had no history of atopic dermatitis. Overall, dupilumab was proven effective in rapidly improving itch and sleeplessness, with early score reduction in both dedicated NRS measures that was detected after 4 weeks, with a progressive amelioration at weeks 16 and 36. Symptom improvement was associated with reduction of erythema and infiltration of CNPG lesions, as demonstrated by the increasing number of patients with reduced IGA score throughout the observation period. We observed response to dupilumab therapy as early as week 4, obtaining amelioration of itching, disease severity, and quality of life. This finding

confirmed a marked and rapid reduction of both itching and DLQI score in dupilumab-treated CNPG patients, detected during the first weeks of therapy.^{15,16,24} Zhai et al¹⁷ reported a rapid improvement of itch after the first 2 weeks of dupilumab therapy, showing a mean reduction of NRS itch intensity of 7.89 (SD 2.93; mean baseline NRS itch intensity 9.11, SD 1.05). Almustafa et al¹⁶ investigated pruritus and quality of life in 3 patients, using an itch intensity score, itch-related quality of life, and DLQI. A marked and sustained improvement of DLQI score was observed by week 2, whereas itch intensity and itch-related quality of life improved by week 4. Napolitano et al¹⁹ described a rapid and marked reduction of both DLQI and pruritus visual analog scale scores after 16-week dupilumab therapy (mean baseline DLQI score 18.6 [SD 5.26] versus 3 [SD 2.34] at week 16, $P < .001$; mean baseline pruritus VAS score 9.15 [SD 0.88] versus 2.75 [SD 0.7] at week 16, $P < .001$) in 9 dupilumab-treated CNPG patients. Our population showed similar mean baseline values of both DLQI score (baseline 21.0 [SD 4.0]) and NRS itch score (8.9 [SD 1.0]), which decreased to 4.6 and 2.7, respectively, achieving values at week 16 in line with those of this previously published study.¹⁹

After 16 weeks of treatment, most patients (17/24; 70.8%) were classified as having mild or very mild scores (IGA score 1/2), and 3 of 10 patients achieved 36 weeks of therapy with complete remission. Additionally, treatment effectiveness on pruritus and skin manifestations led to an improvement of quality of life (DLQI score reduction). Treatment response was maintained as long as after 36 weeks of therapy, similar to results of a recent multicenter study considering retrospectively 16 patients affected by CNPG who were treated with dupilumab, and reporting clinical response over pruritus at 3 months (NRS score for itch median from 8.5 to 3.0) and a subsequent reduction of skin lesions, with 50% of patients (6/12) experiencing total remission of disease at 6 months.²⁴

Dupilumab was demonstrated to be safe in our population of patients affected by CNPG because no serious treatment-emergent adverse events were reported. The most common adverse event was conjunctivitis (8/27; 29.6%), occurring within the first weeks of therapy (reported at week 4 by 7 of 8 patients). All cases of conjunctivitis were mild and resolved with topical therapy without interrupting dupilumab treatment.²⁸ This rate of conjunctivitis observed in our population is in line with clinical outcomes derived from trials testing efficacy and safety of dupilumab for the treatment of atopic dermatitis patients, which detected conjunctivitis in up to 28% of dupilumab-treated patients.²⁹⁻³¹

Although our study included the largest CNPG population, to our knowledge, who were undergoing dupilumab therapy, it has some limitations. First, there was no validated severity assessment tool at the initial data collection. This limitation was also detected among other clinical studies evaluating dupilumab response in CNPG patients because there was no consistency in the methods and assessment tools used. Studies evaluated efficacy with different tools and at different times, underscoring a lack of both validated and simple tools for the assessment of CNPG severity. Second, the limited cohort of treated patients allowed only a descriptive analysis of the data. Third, the study was limited by the short-term observation period considered.

In conclusion, in our cohort of 27 CNPG patients, dupilumab was proven effective in reducing itch and improving CNPG skin lesions. Demonstrating dupilumab effectiveness in treating CNPG in patients without an atopic background, this study may provide additional evidence of a potential pathogenic role of the Th2 pathway in mediating itching in CNPG, regardless of the association with atopic dermatitis. Placebo-controlled randomized prospective studies are under way to definitively describe the therapeutic value of dupilumab in CNPG patients.

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