

Effectiveness of Dupilumab for the Treatment of Generalized Prurigo Nodularis Phenotype of Adult Atopic Dermatitis

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Background: Generalized prurigo nodularis (GPN) is a debilitating, inflammatory skin disease characterized by chronic pruritus, signs of prolonged scratching, and multiple pruriginous papules and nodules. Recent studies identified several forms of GPN as a clinical phenotype of adult atopic dermatitis (AD).

Objective: The aim of the study was to evaluate the effectiveness of dupilumab (D) in adults affected by persistent AD showing a clinical feature of GPN.

Methods: A retrospective study was performed on adult patients affected with GPN clinical variant of AD, treated with D from July 2018 to March 2019. Atopic dermatitis severity was evaluated using the Eczema Area and Severity Index, visual analog scales ranging from 0 to 10 for pruritus, and Dermatology Life Quality Index.

Results: Ninety AD patients (52 males [57.7%]; mean age = 44.6 years; range = 18–66 years) were treated with D. In 9 (10.0%) of 90 cases, GPN pattern was observed. A significant improvement in Eczema Area and Severity Index, Dermatology Life Quality Index, and pruritus visual analog scale score was observed after treatment with D.

Conclusions: Generalized prurigo nodularis is currently considered to be a rather common clinical pattern of adult AD. Dupilumab can be an efficacious treatment of this condition, especially in cases where history of atopy is recorded and conventional treatments are ineffective.

Generalized prurigo nodularis (GPN) is a debilitating skin disease that usually appears at age 40 to 50.^{1,2} Generalized prurigo nodularis consists of intense, chronic pruritus associated with signs of prolonged scratching, including erythematous or brown-black papules and nodules.² The pathogenesis of GPN is largely unknown.² For a long time, it has been supposed that GPN was a neurodermatitis resulting in an itch/scratch cycle, sometimes associated with atopic eczema, cutaneous xerosis, hepatic or renal failure, diabetes, or psychiatric disorders³; furthermore, hypertrophy of cutaneous nerve fibers is a common histologic finding.² In the past years, some authors proposed that GPN may be identified as a clinical phenotype of adult atopic dermatitis (AD).^{4–6} Diagnosing atopic dermatitis is relatively simple in adults whose AD dates since childhood (persistent AD).^{7–10} However, it is difficult to diagnose

when it appears in adulthood (adult-onset AD) and when the clinical presentation is atypical. Indeed, adult AD is characterized by pronounced clinical heterogeneity.⁵ The disease often deviates from the classic pattern of flexural dermatitis, and there are forms of presentation that are specific to adults, such as head-and-neck dermatitis, chronic eczema of the hands, multiple areas of lichenification, or prurigo.⁵ In a Chinese series, approximately 30% of adult patients with AD presented with GPN clinical variant.⁶ Furthermore, drugs used for adult AD have been proposed also for the treatment of GPN, namely, topical corticosteroids, phototherapy, methotrexate, and cyclosporine.¹¹ The efficacy of these treatments is variable, and the long-term management for some patients is difficult.¹¹ Recently, dupilumab (D), a fully human monoclonal immunoglobulin G antibody that links the shared α subunit receptor site for interleukin 4 (IL-4) and IL-13, has been successfully used in some patients with GPN.^{1,12,13}

The aim of this retrospective study was to evaluate the effectiveness of D in adults affected by persistent AD showing a clinical feature of GPN.

MATERIALS AND METHODS

A retrospective study was performed on white adult (≥ 18 years) patients affected with GPN clinical variant of AD, treated with D

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attending the dermatology units of 2 Italian university hospitals (Napoli and Catanzaro), from July 2018 to March 2019. For each patient, the following data were evaluated: (a) personal and demographic data, (b) AD past and current history, (c) disease severity, (d) comorbidities, and (e) previous and current systemic treatments. Disease severity was evaluated before treatment (t0) and 16 weeks after the beginning of treatment with D (t1) using Eczema Area and Severity Index (EASI), visual analog scales (VASs) ranging from 0 to 10 (where "0" means "doesn't itch at all" and "10" means "itch is worse than ever") for pruritus, and Dermatology Life Quality Index (DLQI).^{14,15} Exclusion criteria were other skin or internal disorders that might cause pruritus, cognitive impairment preventing completion of VAS scale and DLQI, or psychiatric diseases that could alter the subjective perception of itch.

The study was conducted following the principles of the Declaration of Helsinki. Unpaired Student *t* test was used to calculate statistical differences. *P* < 0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism 4.0 (GraphPad Software Inc, La Jolla, CA).

RESULTS

Ninety AD adult patients (52 males [57.7%]; mean age = 44.6 years; range = 18–66 years) were treated with D with mean $\pm$ SD therapy duration of 18.6 ± 3.2 weeks. Persistent AD was more common than adult-onset disease. Indeed, 67.8% (61/90) of patients experienced persistent AD, whereas in 32.2% (29/90), AD had directly started in adult age. Seventy-two (80%) of 90 patients were affected by 1 or more atopic comorbidities (allergic rhinitis, asthma, and allergic conjunctivitis above all with 41.2%, 23.1%, and 15.7%, respectively). In 9 (10.0%) of 90 cases, GPN pattern was observed (Table 1; Fig. 1). They were 5 females and 4 males with a mean age of 50.1 years (range = 31–63 years). All the 9 patients experienced persistent AD, with the mean $\pm$ SD age at symptom onset being 1.4 ± 4.2 years. The total immunoglobulin E serum level was above normal in all patients (mean = 1555 kU/L; range = 657–2269 kU/L). The most common atopic comorbidity was

rhinitis (88.9%), followed by asthma (55.6%) and conjunctivitis (33.4%). Treatment with topical steroids and systemic antihistamines had failed in all patients. Cyclosporine (8/9, 88.9%) and narrowband UV-B therapies (5/9 [55.6%]) represented the most common previous systemic treatments, followed by methotrexate 20 mg weekly (4/9 [44.5%]). These treatments in all cases led to no or only slight improvement of skin lesions. The 9 GPN patients were treated with D administered in the standard dosing regimen (600-mg induction dose and 300 mg every 2 weeks thereafter). The evaluation of the results was made after 16 weeks of treatment. In all the patients, a marked clinical improvement was observed (Fig. 1), confirmed by the significant improvement in EASI (mean $\pm$ SD = 30.5 ± 5.68 at t0 vs 8 ± 2.59 at t1, *P* < 0.001), DLQI (mean $\pm$ SD = 18.6 ± 5.26 at t0 vs 3 ± 2.34 at t1, *P* < 0.001), and pruritus VAS score (mean $\pm$ SD = 9.15 ± 0.88 at t0 vs 2.75 ± 0.7 at t1, *P* < 0.001) values. No adverse events were reported. No patient dropped out.

DISCUSSION

Atopic dermatitis in adults is characterized by marked clinical heterogeneity.⁵ Indeed, using the current diagnostic criteria for AD, 11% to 22% of adult AD patients could be not detected.¹⁶ Therefore, clinician's experience is fundamental for a proper differential diagnosis.¹⁰ The most frequent clinical presentations of adult AD are flexural dermatitis with involvement of the face and neck, as well as chronic hand eczema.^{9,17} However, GNP is a quite frequent clinical pattern.^{6,9} In 2014, Werfel et al⁴ suggested that the clinical features of AD vary depending on the stage (acute or chronic) of the disease and the age of the patients, pointing to GNP as a clinical form of chronic adult AD. Some authors report that prurigo features are more common in Asian and African patients.^{18–20} Approximately 30% of adults with AD presented with GPN in a Chinese series of patients.⁶ The concept that GPN is a clinical variant of AD may also be supported by some studies that demonstrated in the epidermis of prurigo nodule some typical aspects of AD pathogenetic profile, such as T_H2 immunologic signature with STAT6 activation and increased expression of IL-4, IL-13, and interferon γ .²¹ Our study showed that D treatment reduces

TABLE 1. Clinical Features of Atopic Patients With GPN Pattern

Patients	Sex	Age, y	Pattern AD	Concomitant Conditions	Ineffective Therapies	EASI (t0)	EASI (t1)
1	F	32	Persistent	Rhinitis and asthma	TCS, hydroxyzine dichlorhydrate, Nb-UVB, CsA,	25	10
2	F	62	Persistent	Asthma	TCS, hydroxyzine dichlorhydrate, Nb-UVB, CsA, MTX	28	10
3	M	53	Persistent	Rhinitis, asthma, conjunctivitis	TCS, hydroxyzine dichlorhydrate, CsA, MTX	25	8
4	M	61	Persistent	Rhinitis	TCS, hydroxyzine dichlorhydrate, Nb-UVB, CsA	38	9
5	F	57	Persistent	Rhinitis and asthma	TCS, hydroxyzine dichlorhydrate, Nb-UVB	41	3
6	F	63	Persistent	Rhinitis, conjunctivitis	TCS, hydroxyzine dichlorhydrate, CsA	26	5
7	M	31	Persistent	Rhinitis	TCS, hydroxyzine dichlorhydrate, CsA	29	9
8	M	42	Persistent	Rhinitis	TCS, hydroxyzine dichlorhydrate, Nb-UVB, CsA, MTX	32	7
9	F	50	Persistent	Rhinitis, asthma, conjunctivitis	TCS, hydroxyzine dichlorhydrate, CsA, MTX	31	11

CsA indicates cyclosporine; F, female; M, male; MTX, methotrexate; Nb-UVB, narrowband UV-B; TCS, topical corticosteroids.

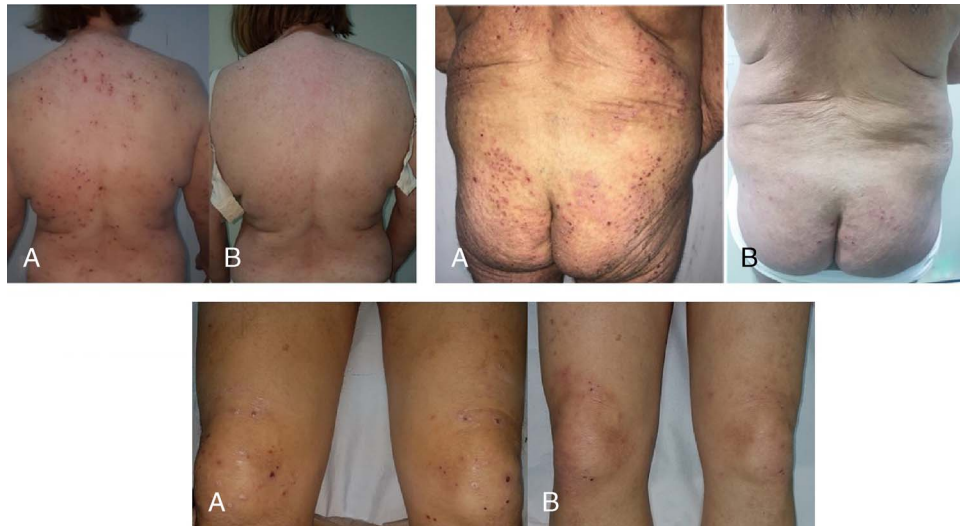


Figure 1. Patients affected with GPN variant of adult AD before treatment with D (A) and after 16 weeks of treatment with D (B).

global severity and pruritus and improves quality of life in a group of adult patients with GPN pattern of AD. As a consequence, we hypothesize that this efficacy is due to the fact that in AD patients with a long history of disease and intense itching GPN is not a distinct clinical entity but a phenotype of AD. Recently, Calugareanu et al¹² reported a case of an atopic patient presenting a dramatic improvement of GPN after 3 months of D treatment. In 2018, Beck et al¹ described 3 patients with longstanding GPN who were treated with D with reduction of symptoms and lesions within 12 weeks of treatment. However, D was added to other treatments, and data on patients' history of AD were missing.¹ Mollanazar et al¹³ described 4 cases of GPN successfully treated with D, with only 1 patient with a history of AD. However, the effectiveness of the drug was reported at different intervals (1, 2, 4, and 12 weeks, respectively).¹³

CONCLUSIONS

Generalized prurigo nodularis is currently considered as a rather common clinical pattern of adult AD. Therefore, we believe that clinicians should consider D as an efficacious treatment of GPN, especially in cases where history of atopy is recorded and conventional treatments are ineffective. On the other hand, further experiences on a larger number of GPN patients are needed to better evaluate this therapeutic option.

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