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LETTER TO THE EDITOR

Long-term therapeutic response to dupilumab in patients affected by prurigo nodularis: A real-world retrospective study

Dear Editor,

Scarce data related to the clinical effectiveness of dupilumab in patients with chronic prurigo nodularis (CPN) have been reported in a real-world setting.[1,2] We retrospectively analysed clinical and demographic features of 64 adult patients affected by CPN who underwent systemic treatment with dupilumab, assessing long-term effectiveness and safeness of dupilumab (Table 1). Prior to starting dupilumab, 75% of patients showed a high disease burden, with moderate-to-severe skin manifestations (investigator global assessment [IGA]-CPN staging: 3–4), severe itch (mean itch-numeric rating scale (itch-NRS): 8.8 ± 1.1), excoriation in at least 26% of total CPN lesions (IGA-CPN activity score: 3–4)[3] in 71.9% of patients (Table 2), marked impairment of patients' quality of life (mean dermatology life quality index [DLQI] score: 22.7 ± 4.8) and sleep disturbances (mean sleep-NRS score: 8.2 ± 1.6).

Systemic corticosteroids and cyclosporine were previously prescribed with no clinical benefit in 78.1% and 51.6% of patients, respectively (Table 1). Other systemic therapies, including methotrexate and azathioprine, were previously interrupted because of a partial or poor control of the disease (Table 1). After 16 weeks of dupilumab treatment, we detected a marked improvement in signs and symptoms of CPN, with a significant reduction of both patient- and physician-reported outcomes compared with baseline (Table 2). Most patients (85%) experienced a substantial decrease in itch severity (itch-NRS reduction ≥4) by week 16, with further improvement by week 32 (97.5%) and subsequent maintenance of the clinical response throughout the study (Table 2). A marked reduction in the number of nodules and the associated excoriation was observed by Week 16 (IGA CPNs 0–1: 21.9%; IGA CPNa 0–1: 72%), with sustained improvement thereafter (IGA CPNs 0–1: 60.9%; IGA CPNa 0–1: 57.8% at week 52). Lower scores of DLQI were detected at the follow-up visits compared with baseline, obtaining an increasing percentage of patients who achieved a ≥4-point reduction in baseline DLQI score and/or an absolute DLQI score of 0–1 (Table 2). The comparison between patients with or without concomitant atopic diathesis revealed similar clinical benefits obtained by dupilumab with a significantly

TABLE 1 Demographic and clinical features of the study patient population at baseline.

Item	Value
Sex	
Male, *n* (%) patients	24 (37.5)
Female, *n* (%) patients	40 (62.5)
Age in years (mean ± SD)	65.3 ± 12.5
Age at the onset of PN in years (mean ± SD)	51.3 ± 16.7
Age at the diagnosis in years (mean ± SD)	59.3 ± 14.3
Diagnostic delay (mean ± SD)	6.2 ± 10.6
BMI (mean ± SD)	25.24 ± 3.98
Patients with BMI > 30, *n* (%) patients	7/48 (14.6)
IgE total count (mean ± SD)	400.6 ± 1308.4
Patients with IgE > 100, *n* (%) patients	43/51 (84.3)
Eosinophil count (mean ± SD)	283.5 ± 385.9
Patients with abnormal eosinophil count (≥500 per mm^3), *n* (%) patients	11/64 (17.2)
Atopic comorbidities, *n* (%) patients	41 (64.1)
Atopic dermatitis, *n* (%) patients	37 (57.8)
Allergic asthma, *n* (%) patients	8 (12.5)
Allergic rhinitis, *n* (%) patients	22 (34.4)
Allergic conjunctivitis, *n* (%) patients	5 (7.8)
Familiarity for atopy, *n* (%) patients	14 (21.9)
Cardiovascular comorbidities, *n* (%) patients	19 (29.7)
Psychiatric-neurological comorbidities, *n* (%) patients	5 (7.8)
Systemic autoimmune disease, *n* (%) patients	6 (9.4)
Kidney failure, *n* (%) patients	2 (3.1)
Current/previous history of malignancies, *n* (%) patients	4 (6.3)
Chronic infections, *n* (%) patients	2 (3.1)
Previous therapy, *n* (%) patients	
Systemic steroids, *n* (%) patients	50 (78.1)
Discontinuation for ineffectiveness, *n* (%) patients	36 (72.0)
Cyclosporine, *n* (%) patients	31 (51.6)
Discontinuation for ineffectiveness, *n* (%) patients	18 (58.1)
Discontinuation for adverse events, *n* (%) patients	5 (16.1)
Other systemic therapies, *n* (%) patients	12 (18.7)
Methotrexate	4 (6.2)
Antihistamines	4 (6.2)
Azathioprine	2 (3.1)
Phototherapy	2 (3.1)

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TABLE 2 Assessment of disease severity, adverse events and reason of discontinuation throughout the observation period.

Overall population					
	Baseline (BL)	**Week 16 (W16)**	**32 weeks (W32)**	**52 weeks (W52)**	**104 weeks (W104)**
N. of observed patients	64	62	52	40	33
IGA CPNs score[a] (mean ± SD)	3.3 ± 0.9	2.0 ± 1.0*	1.6 ± 0.9*	0.9 ± 0.4*	0.9 ± 0.4*
Patients achieving IGA CPNs 0–1 during treatment (*n*, %)	–	14 (21.9)	23 (35.9)	39 (60.9)	30 (46.9)
Patients with atopic diathesis achieving IGA CPNs 0–1 during treatment (*n*, %)	–	15 (40.5)**	17 (60.7)**	18 (94.7)	8 (88.9)
Patients without atopic diathesis achieving IGA CPNs 0–1 during treatment (*n*, %)	–	2 (7.7)**	6 (27.3)**	20 (100.0)	21 (100.0)
IGA CPNa score[b] (mean ± SD)	2.8 ± 0.8	1.0 ± 0.5*	1.0 ± 0.5*	1.0 ± 0.6*	0.9 ± 0.3*
Patients achieving IGA CPNa 0–1 during treatment (*n*, %)	–	46 (71.9)	43 (67.2)	37 (57.8)	29 (45.3)
Itch-NRS[c] (mean ± SD)	8.8 ± 1.1	3.1 ± 2.1*	2.2 ± 1.6*	1.5 ± 1.5*	1.2 ± 1.2*
Sleep-NRS[d] (mean ± SD)	8.2 ± 1.6	2.1 ± 1.8*	1.8 ± 1.3*	1.2 ± 1.6*	1.0 ± 1.0*
DLQI score[e] (mean ± SD)	22.7 ± 4.8	4.2 ± 1.9*	2.3 ± 1.9*	1.2 ± 1.4*	0.9 ± 0.3*
DLQI = 0–1 (*n*, %)	0/45 (0)	3/41 (7.3)	15/41 (36.6)	30/33 (90.9)	30/30 (100)
≥4-point improvement itch-NRS (*n*, %)	–	45/53 (84.9)	48/50 (96.0)	39/40 (97.5)	32/33 (97.0)
≥4-point improvement sleep-NRS (*n*, %)	–	39/44 (88.6)	41/43 (95.3)	33/33 (100)	29/29 (100)
≥4-point improvement DLQI (*n*, %)	–	39/39 (100)	38/38 (100)	32/32 (100)	26/26 (100)
N. of dropped outpatients (reason)	–	2 (1 patient decision; 1 lost-to-follow-up)	1 (clinical remission)	2 (1 for AEs; 1 for patient decision)	–
Adverse events	–	1 case of telogen effluvium	1 case of arthralgias; 1 case of conjunctivitis/ocular disturbances; 1 case of injection site reaction	1 case of arthralgias; 1 case of acute respiratory failure	1 case of arthralgias; 1 case of oral candida infection; 1 case of asthenia

Note: Values are presented as mean ± Standard Deviation (SD) or *n* (number) and (%) (percentage), with missing data handled through an 'as observed' analysis.

[a]IGA CPNs (Investigator Global Assessment Chronic Prurigo Nodularis Staging): a 5-points physician reported outcome assessing the number of nodules (0 = Clear), no pruriginous lesions (0 lesions); 1 = almost clear, rare palpable pruriginous lesions (approximately 1–5 lesions); 2 = mild, few palpable pruriginous lesions (approximately 6–19 lesions); 3 moderate, many palpable pruriginous lesions (approximately 20–100 lesions); 4 = severe; abundant palpable pruriginous lesions (over 100 lesions).

[b]IGA CPNa (Investigator Global Assessment Chronic Prurigo Nodularis Activity): a 5-points physician reported outcome assessing the percentage of excoriated nodules (0 = Clear); no pruriginous lesions have excoriations or crusts; 1 = almost clear; very small proportion of pruriginous lesions have excoriations or crusts (up to approximately 10% of all pruriginous lesions) 2 = mild; minority of pruriginous lesions have excoriations or crusts (approximately 11%–25% of all pruriginous lesions) 3 Moderate Many pruriginous lesions have excoriations or crusts (approximately 26%–75% of all pruriginous lesions) 4 Severe Majority of pruriginous lesions have excoriations or crusts (approximately 76%–100% of all pruriginous lesions).

[c]Itch NRS (Numeric Rating Scale): a patient reported outcome ranging from 0 to 10 evaluating the worst itching experienced in the past 3 days.

[d]Sleep NRS (Numeric Rating Scale): a patient reported outcome ranging from 0 to 10 evaluating the worst sleep disturbance experienced in the past 3 days.

[e]DLQI, (Dermatology Life Quality Index): a patient-reported outcome, ranging from 0 to 30, that assesses the burden of disease on the patient's quality of life over the past 7 years.

*$p < 0.001$ for comparison between baseline and each timepoint values.

**$p < 0.05$ for comparison between CPN patients with or without atopic diathesis.

more rapid reduction of IGA CPNs score and a significantly higher rate of patients achieving IGA CPNs of 0–1 in patients with concomitant atopic diathesis. Similarly, patients with elevated values of baseline IgE (>100 UI/mL) achieved a significantly lower itch-NRS at Week 16 than patients with normal baseline IgE level (≤100 UI/mL) (2.9 ± 2.1 versus 4.4 ± 1.6, $p = 0.043$).

Overall, nine adverse events were reported during the observation period with a relatively more frequent detection of arthralgias (Table 2); four patients withdrew treatment and one was lost to follow-up (Table 2).

Initial trials[3] and previous real-world experiences did not assess treatment response beyond 24 weeks.

In our study we considered a long-term observation period lasting up to 104 weeks of treatment to assess dupilumab effectiveness and safeness and the limited number of patients who reached this timepoint validated some observations of delayed responses up to 1 year, demonstrating that the complete resolution of CPN could be achievable through a long-term treatment. Another strength of this study was represented by the largest real-world cohort of CPN patients treated with dupilumab, whose response was holistically evaluated by multiple physician- and patient-oriented tools. Our findings are consistent with those described in phase 3 trials[4] but suggesting a favourable effectiveness and safeness in the long-term period with a sustained and progressive amelioration of CPN manifestations beyond 24 weeks. In line with one previous study,[1] our findings suggested an enhanced and more rapid response in CPN patients with atopic diathesis that may likely reflect an enhanced type 2 inflammatory signal that could predominantly characterize the immune endotype of CPN, exceeding other immune signals.[5,6]

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CONFLICT OF INTEREST STATEMENT

Outside of the submitted work, authors declare the following conflicts of interest: none declared for the authors with the exception of Andrea Chiricozzi has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Boerhinger-Ingelheim, Bristol Myers Squibb, Galderma, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme, and UCB-pharma, outside the submitted work. Giampiero Girolomoni has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Merck Serono, Novartis, Pfizer, Samsung and Sanofi. Niccolò Gori served as advisory board member and received honoraria for lectures for AbbVie, Sanofi, and Leo-Pharma. Ketty Peris has served on advisory board and received honoraria for lectures and/or research grants for Abbvie, Almirall, Lilly, Galderma, Leo Pharma, Pierre Fabre, Novartis, Sanofi, Sun Pharma, Janssen.

DATA AVAILABILITY STATEMENT

Enquiries related to the data generated or analysed during this study can be directed to the corresponding author.

ETHICS STATEMENT

The patients included in this study have given written informed consent to publication of their case details.

ETHICAL APPROVAL

Approval of this study was obtained by the Local Ethics Committee—Comitato Etico Territoriale Lazio Area 3, Prot ID: 5909.

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