SHORT COMMUNICATION

Four Cases of Prurigo Nodularis Requiring Nemolizumab due to Persistent Pruritus or Lesions after Dupilumab Treatment

Yoshihito MIMA, Masako YAMAMOTO and Ken IOZUMI
Department of Dermatology, Tokyo Metropolitan Police Hospital, Tokyo, Japan. E-mail: yoshihito11.mima@gmail.com
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Prurigo nodularis (PN) is a chronic inflammatory skin disorder comprising itchy papules, pustules, and nodules. Repeated scratching worsens these, contributing to chronicity and progression (1). PN is associated with conditions such as atopic dermatitis, psychiatric disorders, kidney failure, and diabetes (2). Its pathogenesis is driven by persistent pruritus and repetitive scratching, progressing the "itch–scratch cycle". While the exact mechanisms remain unclear, immune and neural dysregulation are key (3). PN lesions contain immune cells such as eosinophils, macrophages, and T cells, with Th2-driven inflammation predominant (4). Th2 cytokines are upregulated, activating peripheral nerve receptors and triggering pruritus (5). PN also results from altered nerve fibre density and increased neuropeptides caused by neurological changes (6). Treatments include topical corticosteroids, topical calcineurin inhibitors, phototherapy, systemic agents (e.g., cyclosporine), and oral antidepressants (2). Recently, biologic agents selectively inhibiting Th2-associated cytokines, such as interleukin (IL)-4/13/31, have shown promise for PN (7).

In 2 phase 3 trials of dupilumab (PRIME/PRIME2), at week 24, 60.0% of patients receiving dupilumab achieved a ≥4-point improvement in the Peak Pruritus Numerical Rating Scale (PP-NRS), versus 18.4% receiving placebo ($p<0.001$). Moreover, 48.0% and 44.9% of patients receiving dupilumab achieved a Prurigo Nodularis Investigator's Global Assessment (PN-IGA) of 0/1 in PRIME and PRIME2 respectively, compared with 18.4% and 15.9% receiving placebo ($p<0.001$). These results led to dupilumab's approval, with efficacy confirmed in post-marketing studies (8, 9). Similarly, nemolizumab demonstrated significant efficacy in the OLYMPIA2 trial. At week 16, 56.3% of patients receiving nemolizumab achieved a ≥4-point improvement in PP-NRS, vs 20.9% receiving placebo ($p<0.001$). Additionally, 37.7% of patients receiving nemolizumab achieved a PN-IGA of 0/1, vs 11.0% receiving placebo ($p<0.001$). Based on these findings, nemolizumab was approved by the Food and Drug Administration in 2024 (10, 11). Notably, nemolizumab showed rapid onset of action, significantly improving PP-NRS and sleep disturbances within days (12). However, its post-marketing data remain limited, and no head-to-head trials with dupilumab have been conducted. Herein, we report 4 cases of PN that exhibited insufficient improvement in skin lesions or pruritus following dupilumab, leading to the consequent administration of nemolizumab.

CASE SERIES

Four patients with PN, despite receiving dupilumab (initially 600 mg, then 300 mg approximately biweekly), experienced persistent pruritus or skin lesions and subsequently switched to nemolizumab at their request. All exhibited multiple pruritic nodules on the extremities or trunk (**Figs 1**A, **2**A). Patient characteristics

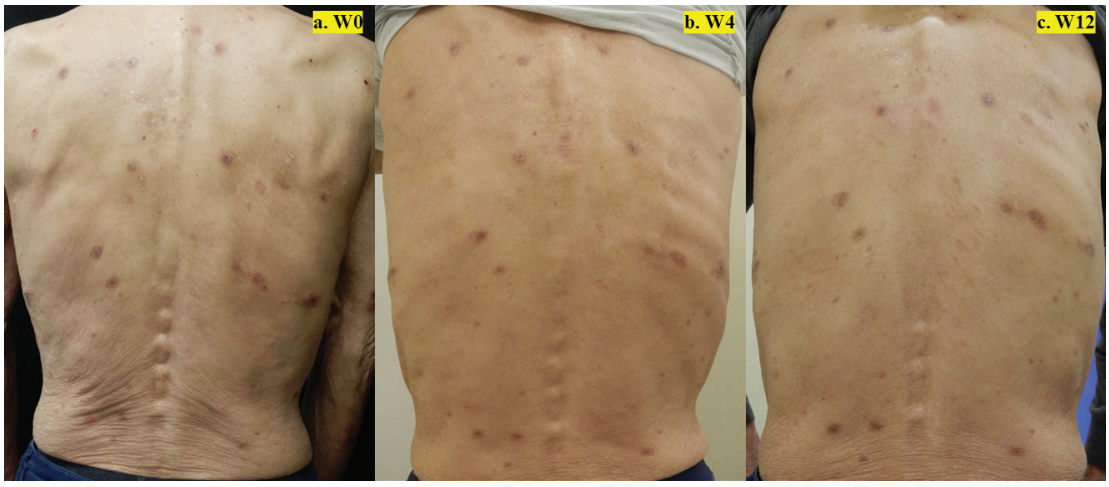

Fig. 1. Clinical features of Patient 1 with prurigo nodularis who switched to nemolizumab after 12 weeks of dupilumab treatment due to persistent pruritus. (A) Baseline back lesions at the start of nemolizumab treatment. Before nemolizumab, dupilumab had led to partial flattening of the nodules, but numerous palpable lesions remained (PN-IGA 4), and pruritus remained severe (PP-NRS 7). (B) At Week 4, previously palpable nodules showed further flattening and signs of improvement (PN-IGA 3), though pruritus persisted (PP-NRS 5). (C) At Week 12, most nodules had flattened and evolved into post-inflammatory hyperpigmentation (PN-IGA 2), while pruritus remained stable (PP-NRS 6).

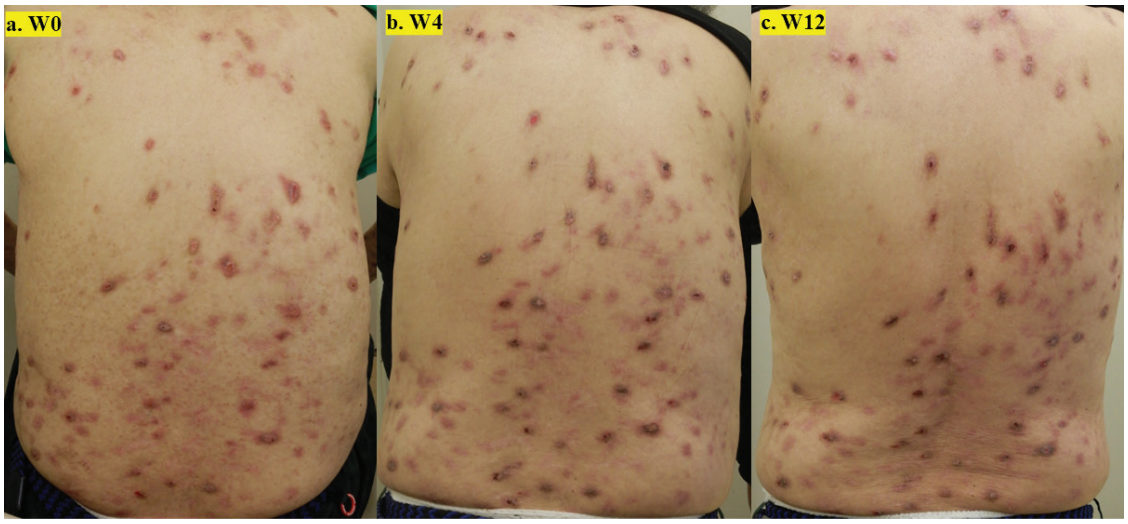

Fig. 2. Clinical features of Patient 3 with prurigo nodularis who switched to nemolizumab after 13 weeks of dupilumab treatment due to persistent pruritus or skin lesions. (A) Baseline back lesions at the start of nemolizumab treatment. Before nemolizumab, despite prior dupilumab treatment, the nodules remained largely unchanged, with numerous palpable lesions (PN-IGA 4), and pruritus was extremely severe (PP-NRS 10). (B) At Week 4, the nodules showed no significant flattening and remained stable (PN-IGA 4), but pruritus improved markedly (PP-NRS 5). (C) At Week 12, some nodules showed signs of shrinkage, but many remained palpable (PN-IGA 4). However, pruritus continued to improve (PP-NRS 3).

are presented in Table SI. The mean age was 79 years (range: 73–84). All had lesions on the extremities, and 2 had additional trunk involvement. None had a history of atopic dermatitis or renal dysfunction; 1 had cardiovascular disease, 2 had diabetes, and 3 were smokers. The dupilumab treatment period ranged from 10 to 14 weeks. Owing to refractory pruritus and skin lesions, patients were dissatisfied with dupilumab and opted to transition to nemolizumab (initial 60 mg, then 30 mg monthly). The treatment course in Patients 1 and 3 from baseline to 12 weeks is shown in Figs 1 and 2. Mean PP-NRS prior to dupilumab therapy was 9 (range: 8–10), and mean PN-IGA was 3.5 (range: 3–4). At the initiation of nemolizumab, mean PP-NRS was 7.0 (range: 4–10) and changed as follows: week 4: 3.75 (range: 2–5), week 8: 2.5 (range: 0–6), and week 12: 2.75 (range: 0–6). At week 12, all showed PP-NRS similar to or slightly worse than at week 8. However, 3 patients achieved a ≥4-point PP-NRS improvement. The mean PN-IGA at baseline was 3.5 (range: 3–4) and changed as follows: week 4: 2.75 (range: 2–4), week 8: 2.5 (range: 1–4), and week 12: 2.25 (range: 1–4). Gradual improvement in PN-IGA was observed, with 1 patient achieving PN-IGA 0/1. No adverse events were observed. Three patients continued nemolizumab treatment; 1 discontinued at week 20 because of persistent pruritus despite lesion regression.

DISCUSSION

Dupilumab significantly improved PP-NRS and PN-IGA in clinical trials, confirming that Th2 cytokines (IL-4/13) drive PN and suggesting dupilumab disrupts the itch–scratch cycle (4, 8, 9). However, 40–50% of patients showed incomplete symptom improvements, highlighting the need for additional treatments (8, 9). Nemolizumab also significantly improved PP-NRS and PN-IGA (11). IL-31, a key driver of fibrosis and neuroinflammation in PN, is blocked by nemolizumab, potentially preventing disease progression (11,13). Comparing nemolizumab and dupilumab is difficult owing to differences in study design; OLYMPIA2 lasted 16 weeks (less than PRIME/PRIME2) and did not allow topical agents during the trial, unlike dupilumab trials. Nevertheless, nemolizumab significantly improved PP-NRS and PN-IGA, confirming its efficacy (9–11). However, treatment options for dupilumab-refractory PN are unclear. While abrocitinib significantly improved PP-NRS and PN-IGA in patients with PN in an open label Phase 2 study (13), nemolizumab's efficacy in this setting remains unstudied.

In this study, we evaluated 4 patients with PN who, despite a specific period of dupilumab therapy, experienced persistent pruritus or lesions and opted to switch to nemolizumab. After 12 weeks of nemolizumab, PP-NRS improved from 7.0 to 2.75, and PN-IGA improved from 3.5 to 2.25, with 3 patients achieving ≥4-point PP-NRS improvement and 1 achieving PN-IGA 0/1. In clinical trials of dupilumab for PN, efficacy has typically been assessed at 24 weeks. In contrast, our study evaluated treatment response at 10–14 weeks, which may have been too short a duration to fully assess the drug's potential efficacy. However, in all cases, the response to dupilumab was limited at that point, with persistent pruritus prompting the patients' desire to switch to nemolizumab. In clinical practice where nemolizumab is available as an alternative, continuing dupilumab for the full 24 weeks may be challenging for patients experiencing insufficient symptom relief. Additionally, to align with the dupilumab treatment period, we evaluated the efficacy of nemolizumab at 12 weeks. Nonetheless, pivotal clinical trials of nemolizumab assessed outcomes at 16 weeks, and it is possible that further improvements might have been observed with a longer follow-up period. The optimal timing for evaluating the therapeutic efficacy of dupilumab or nemolizumab remains controversial.

PN involves IL-4/13/31. Mouse studies have indicated that IL-31-driven itch persists despite IL-4/13 inhibition (14), possibly explaining why dupilumab may not fully

resolve symptoms if IL-31 remains active. The phase 2 study showing abrocitinib's efficacy in PN may support this hypothesis (13). In addition to underlying conditions such as renal dysfunction, the multifactorial nature of PN, driven by Th2 inflammation but also involving Th1/17 pathways, may influence the clinical course (2, 5, 15). Patients 2–4 were highly satisfied with pruritus improvements; Patient 1, despite persistent itching, expressed certain levels of satisfaction with the regression of lesions. After 6 doses, Patient 1 was content with flattened lesions and discontinued nemolizumab despite refractory pruritus. In contrast, Patients 2–4 continue nemolizumab because of relapse concerns. When to discontinue nemolizumab remains unaddressed, warranting future study.

To our knowledge, no studies have examined switching from dupilumab to nemolizumab for refractory PN. Many patients with PN have persistent symptoms post-dupilumab, highlighting unmet medical needs. This study has limitations, includingcase series with small single-centre samples, no control group, and a short observation period. However, our findings suggest nemolizumab as a potential alternative, but larger studies are needed to confirm its efficacy in dupilumab-refractory PN.

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IRB approval status: This study is a case series of 4 cases, in which both dupilumab and nemolizumab were administered at their approved doses for prurigo nodularis. As all 4 patients provided consent for photographic documentation and article publication, ethical approval was not required.

Conflict of interest disclosures: YM and KI have received lecture fees from Maruho Co., which markets nemolizumab.

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