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Research Article

Dupilumab Therapy of Prurigo Nodularis: A Single-Center, Real-Life Observational Study

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Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by severe itching accompanied by multiple nodules throughout the body. There is currently no effective drug-targeted treatment for PN. Dupilumab is a fully human monoclonal antibody which can suppress the Th2 inflammatory reaction. We aimed to assess the efficacy and safety of dupilumab in PN. There were 29 PN patients who received dupilumab treatment for four months. Serum total immunoglobulin E (Ig E), eosinophil counts, dermatology life quality index (DLQI), and numeric rating scale (NRS) were assessed on patients before and after treatment. We count the vaccination of novel coronavirus pneumonia (COVID-19) in patients and the impact on PN and treatment measures after vaccination. Plotting was performed using GraphPad Prism8, and the statistical analysis was performed using PASW Statistics18. The eosinophil counts in patients higher decreased to normal, and the Ig E levels gradually decreased and tended to normal levels after receiving dupilumab injection. The average DLQI score at the baseline was 23.93 ± 0.66 and decreased to 11.66 ± 0.55 ($P < 0.01$) and 1.83 ± 0.22 ($P < 0.01$) at 1-month and 6-monthfollow-up of treatment, respectively. The average NRS score at the baseline was 9.79 ± 0.08 and decreased to 3.52 ± 0.23 ($P < 0.01$) and 0.31 ± 0.15 ($P < 0.01$) at the 1-month and 6-monthfollow-up of treatment, respectively. Our study shows that dupilumab has achieved good efficacy in PN with few adverse reactions and high safety. We can recommend that patients follow the advice of specialists to be vaccinated and under the condition of stable disease, separated from dupilumab treatment for one week.

1. Introduction

Prurigo nodularis (PN) is a chronic inflammatory skin disease with symmetrical distribution of nodules as typical skin lesions and severe itching as the main symptom [1]. The lesions are typically located in symmetric linear arrangements along the extensor surface, the face and palms are rarely involved, and nodules do not occur in the sites that are not reached by the patient [2]. Histopathological examination of the skin of PN lesions shows a dense infiltration of eosinophils, T lymphocytes, and mast cells that release multiple proinflammatory cytokines [3]; however, the incidence and prevalence of PN are not very clear, but some surveys show that it occurs more frequently in women and the elderly [2] and can also occur in children [4]. The quality of life of patients with this disease is severely reduced, and many studies have found that PN is significantly associated with insomnia, anxiety, and depression [5].

The exact pathogenesis of PN is unclear, but it is currently thought to be related to immune abnormalities caused by T lymphocytes, eosinophils, and mast cells, as well as potential interactions between neurons and neurohumor, resulting in intractable, malignant pruritus scratching cycles which subsequently lead to characteristic pruritic nodules [6]. Immune cells in the skin generate a robust inflammatory response and intense itch by releasing mediators such as interleukin (IL)-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides, and this immune response is central to the pathogenesis of PN [7]. Messenger RNA for the T cell-derived cytokine IL-31 is more abundant in skin lesions of PN when compared with the healthy skin, [8] beyond that, subsets of Th2 cytokines such as IL-4 have also been found to be increased in prurigo-like

skin lesions [9]. Recent studies have shown that the IL-4 receptor is directly expressed on sensory neurons in the dorsal root ganglia of both humans and mice. This receptor is directly activated by expression of type 2 cytokines, such as IL-4, IL-13, and IL-31 [10]. Additionally, many factors are associated with PN, including eczema, psychiatric diagnoses, and chronic diseases such as malignancy, chronic liver and kidney failure, diabetes, and human immunodeficiency virus (HIV) infection [11–13]. PN remains a difficult condition to treat. The treatment of PN is mainly aimed at the underlying immune and neural dysregulation which includes topical acting agents (corticosteroids, anesthetics, calcineurin inhibitors, etc.), systemic neuromodulating agents (gabapentinoids, mu-opioid antagonists, thalidomide, etc.), systemic immunomodulating agents (corticosteroids, cyclosporine, and azathioprine), and phototherapy etc. There are also emerging treatments, such as targeting IL-31, IL-4, and oncostatin m (OSM) beta receptors, in the itch pathogenesis of PN [9, 14].

Dupilumab is a fully human monoclonal antibody that blocks IL-4 receptor subunit α (IL-4Rα) and results in dual inhibition of IL-4 and IL-13 [15]. To date, dupilumab in atopic dermatitis (AD) has proven to be a safe and effective drug for more than 6 months, [16] including elderly patients, also during the Covid-19 pandemic [17–21]. The collective role of Th2-related cytokines in the pathogenesis of PN suggests that dupilumab may be an effective treatment for this disease [15]. The objective of our study was to evaluate the efficacy and safety of off-label use of dupilumab in PN in the real world.

2. Patients and Methods

2.1. Patients. This study collected patients with PN in our center from October 2020 to May 2022. Inclusion criteria are as follows: PN was diagnosed by clinical presentation and skin biopsy; if patients refused to use also topic therapy or if it was ineffective. Exclusion criteria are as follows: receiving and effective treatment with systemic corticosteroids and immunosuppressants; poor patient compliance; hospitalization during treatment for severe allergies, systemic infectious diseases, or other diseases. After obtaining an informed consent from patients and their families, the following information was collected for each patient: demographic and clinical data (sex, age, and disease duration), other comorbidities, and previous medication history.

2.2. Assessments. Laboratory test results for serum total immunoglobulin E (Ig E) and eosinophil counts were collected at the baseline, one and six months after starting treatment. Dermatology life quality index (DLQI) and numeric rating scale (NRS) were determined at the baseline, one and six months after starting treatment. At the same time, the patients were followed up to observe whether there was any discomfort during treatment.

2.3. Medication. All patients were administered an initial dose of 600 mg, subcutaneous injection, followed by a maintenance dose of 300 mg every two weeks. The treatment continued for at least 4 months. There were two female pediatric patients (one 13 and one 14 years old) weighing >60 kg, and experts recommended the initial dose was 600 mg, followed by a maintenance dose of 300 mg every two weeks. Dupilumab can be used in combination with basic therapy and topical therapy in the early stage of PN, and the original therapy can be stopped gradually after dupilumab takes effect and the patient's condition is stable for treatment.

2.4. Regarding the Situation of the Novel Coronavirus Pneumonia (COVID-19) Vaccine. Since COVID-19 swept the world in late 2019, it has seriously threatened human life and health and caused huge medical, financial, and social damage globally. In the absence of specific treatment methods, vaccines are the most effective means of global prevention and control of COVID-19, and countries have invested heavily in vaccine development [22]. According to different research and development strategies, they can be divided into three categories: protein vaccines; gene-based vaccines; and combining protein- and gene-based methods to generate one or more protein antigens in vitro and in vivo, typically represented by live attenuated virus vaccines [23]. Since December 15, 2020, China has started large-scale vaccination work. Inactivated vaccines, adenovirus vector vaccines (type 5 adenovirus vector), and recombinant subunit vaccines (CHO cells) have been used urgently or approved for marketing under certain conditions [24]. Here, we count the vaccination of patients and the impact on PN and treatment measures after vaccination.

2.5. Statistical Analyses. Plotting was performed using GraphPad Prism8, and the statistical analysis was performed using PASW Statistics18. Data represent mean ± sem. Multiple sample means were compared using the analysis of variance with repeated measures design data. Differences between data were considered statistically significant when $P < 0.05$.

3. Results

Twenty-nine patients were finally included in our study. There were 22 males (76%) and seven females (24%). The youngest age was 13 years, the oldest was 86 years, and the average age was 56.55 ± 3.23; the shortest duration of the disease was half a year, and the longest was 20 years, with an average of 4.87 ± 0.94. Four patients (13.79%) had hypertension, two patients (6.90%) had diabetes, one patient (3.45%) had coronary heart disease, and one patient (3.45%) had human immunodeficiency virus (HIV) infection. Among them, three patients (10.34%) had concurrent allergic rhinitis, and 11 patients (37.93%) had previously been diagnosed with eczema. Two patients (6.90%) had a family history of allergic diseases, and one patient (3.45%) had a family history of eczema. Five patients (17.24%) had symptoms of anxiety, three patients (10.34%) had symptoms of depression, and 15 patients (51.72%) had sleep disorders. None of them had taken medication to improve their mental state. With the improvement of the disease during the

treatment, the patient's mental condition improved significantly. Laboratory test results showed that seven patients (24.14%) had eosinophil counts higher than $0.52 * 10^9$/L and six patients (20.69%) had blood Ig E levels higher than normal levels (in adults ≥100 IU/mL, in children 10–15 years old ≥200 IU/mL). The eosinophil counts in these patients decreased to normal levels, and Ig E levels gradually decreased and tended to normal levels after receiving dupilumab treatment. All patients had previously been treated with antihistamines and topical glucocorticoids; 18 patients (62.07%) had received oral and/or intramuscular glucocorticoids, six patients (20.69%) had received oral thalidomide tablets, and four patients (13.79%) had received microneedling. Seven patients (24.14%) had received at least three of the above treatments but only had a short-term therapeutic effect. Patient details are shown in Table 1.

In our study, all patients were treated for at least four months, and the patients with the longest treatment were treated for 8 months. We followed up and observed the DLQI and NRS scores of the patients at the baseline, one month, and six months after starting treatment, respectively. The average DLQI score at the baseline was 23.93 ± 0.66 and decreased to 11.66 ± 0.55 ($P < 0.01$) and 1.83 ± 0.22 ($P < 0.01$) at 1-month and 6-monthfollow-up of treatment, respectively. The average NRS score at the baseline was 9.79 ± 0.08 and decreased to 3.52 ± 0.23 ($P < 0.01$) and 0.31 ± 0.15 ($P < 0.01$) at the 1-month and 6-monthfollow-up of treatment, respectively. The DLQI and NRS scores of the patients are shown in Table 2 (two patients showed moderate improvement in pruritus symptoms). During the treatment, pruritus in two patients (6.90%) (one patient with skin lesions concentrated on the back, and the other patient concentrated on the head, face, neck, and upper limbs) worsened after stopping the four months of treatment for one month, and the condition improved after the maintenance dose was given to continue the injection.

Overall, we observed that the patient's itching symptoms improved significantly (Figure 1), less scratching, improved sleep quality, gradual regression of skin lesions, and residual hyperpigmentation at the primary site after dupilumab treatment. However, there were still some patients with stubborn nodules that subside slowly. We combined liquid nitrogen freezing and microneedling therapy to promote the recovery of skin lesions. Interestingly, we found that regression of nodules in the head was slower in some patients than in the trunk and extremities. The patients in this study had no adverse reactions during treatment. Typical cases are shown in Figures 2 and 3.

In our study, six patients (20.69%) were not vaccinated because of concerns about their condition, 23 patients (79.31%) were vaccinated, and among them, one patient (4.35%) was vaccinated before the disease, two patients (8.70%) reported that the disease tended to aggravate after vaccination, and the remaining 20 patients (86.95%) vaccinated under the advice of doctors and under the condition of stable disease, separated from dupilumab treatment 1 week, and the disease does not worsen. The vaccination status of the patients with COVID-19 is shown in Figure 4.

Table 1: Basic information of patients with prurigo nodularis.

Variables	Value n (%)
Sex	
Male	22 (76%)
Female	7 (24%)
Age	56.55 ± 3.23
Disease duration	4.87 ± 0.94
Comorbidities	
Hypertension	4 (13.79%)
Diabetes	2 (6.90%)
Coronary heart disease	1 (3.45%)
Allergic rhinitis	3 (10.34%)
Eczema	11 (37.93%)
Depression	3 (10.34%)
Anxiety	5 (17.24%)
Sleep disorders	15 (51.72%)
HIV	1 (3.45%)
Family history	
Allergic diseases	2 (6.90%)
Eczema	1 (3.45%)
Laboratory examination	
Elevated eosinophil count	7 (24.14%)
Elevated Ig E levels	22 (20.69%)
Previous treatment	
Antihistamine treatment	29 (100%)
Topical glucocorticoids	29 (100%)
Oral and/or intramuscular injection glucocorticoids	19 (65.52%)
Oral thalidomide	6 (20.69%)
Microneedle therapy	4 (13.79%)

4. Discussion

The pathogenesis of PN is largely related to the enhanced inflammatory response, and several proinflammatory and pruritic cytokines are elevated in PN lesions, including Th2-related cytokines such as the interleukins IL-31 and IL-4 [2]. Dupilumab inhibits the type 2 immune response by blocking the IL-4 and IL-13 pathways, which can be used to break the pruritus cycle of PN and achieve the purpose of treatment [25]. In our study, a retrospective observational study of PN was performed. The real-world data are closer to clinical reality than the strict inclusion and exclusion criteria of clinical trials. Our study showed that a significant reduction was observed in disease severity as measured by NRS and DLQI scores after four months of treatment, and dupilumab has achieved good efficacy in PN with few adverse reactions and high safety. The results of this study are similar to previous studies [14, 25, 26]. It can quickly reduce itching, prevent the appearance of new nodules, and gradually reduce the number of current nodules [14].

PN is often associated with other allergic diseases, such as AD or chronic pruritus of various origins. In recent years, many scholars believe that PN can be regarded as a clinical manifestation of AD [27]. The study by Stander et al. [11] showed that nearly half of PN had atopic predisposition or AD as the single cause of PN or mixed origin. In our study, 11 patients (37.93%) had been diagnosed with eczema in the past, and the conventional treatment was ineffective, long-

Table 2: Patient's DLQI and NRS scores.

Patient	DLQI0	DLQI1	DLQI6	NRS0	NRS1	NRS6
1	18	11	0	10	4	0
2	15	7	0	9	4	0
3	25	15	4	9	4	0
4	27	14	2	10	2	0
5	25	17	2	10	3	0
6	25	13	1	9	3	0
7	27	12	2	10	2	0
8	28	8	2	10	4	0
9	27	12	3	10	2	0
10	24	10	2	10	4	1
11	20	8	1	9	4	0
12	22	15	3	10	2	0
13	26	15	1	10	4	0
14	27	14	1	10	3	0
15	27	10	2	10	2	0
16	27	8	1	10	3	0
17	27	12	1	9	2	0
18	22	14	1	10	5	0
19	23	9	2	10	4	0
20	24	10	2	10	5	1
21	28	14	4	10	4	0
22	21	12	4	10	6	3
23	24	8	2	10	5	0
24	22	9	2	10	1	0
25	16	10	1	10	5	3
26	20	11	1	10	3	1
27	26	18	4	9	4	0
28	23	8	0	10	5	0
29	28	14	2	10	3	0

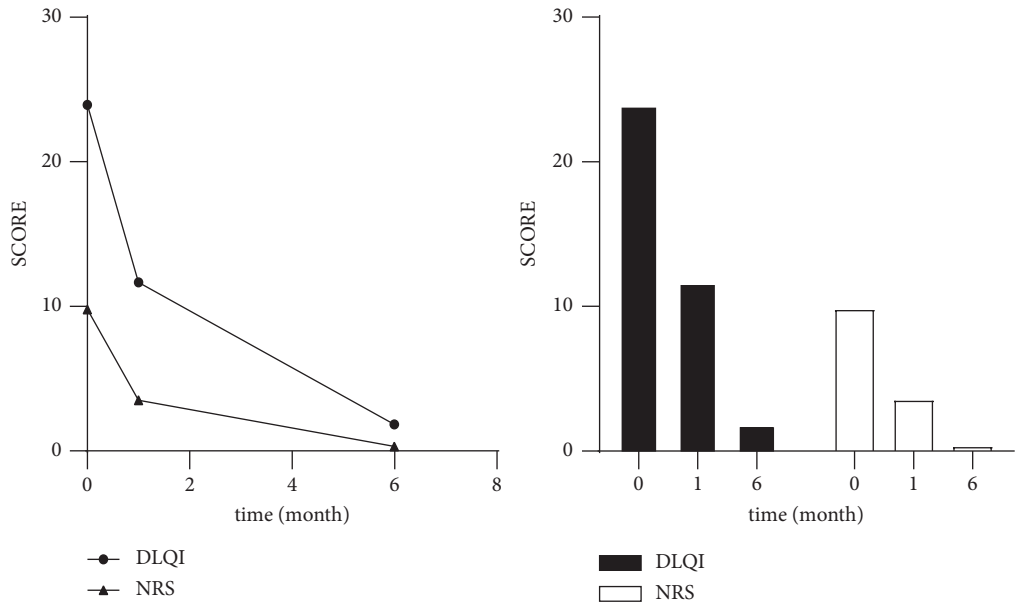

Figure 1: Changes in DLQI and NRS scores of patients.

term repeated scratching of the skin gradually formed nodules.

The efficacy of dupilumab in AD has been confirmed, and it can significantly improve the symptoms of itching, anxiety, and sleep disturbance and improve the quality of life of patients [15]. Although it is not currently approved for PN, our study found that dupilumab can also significantly improve the symptoms of PN, such as itching, sleep disturbance, and anxiety. Compared with AD treatment, the skin lesions did not fully recover after four months of

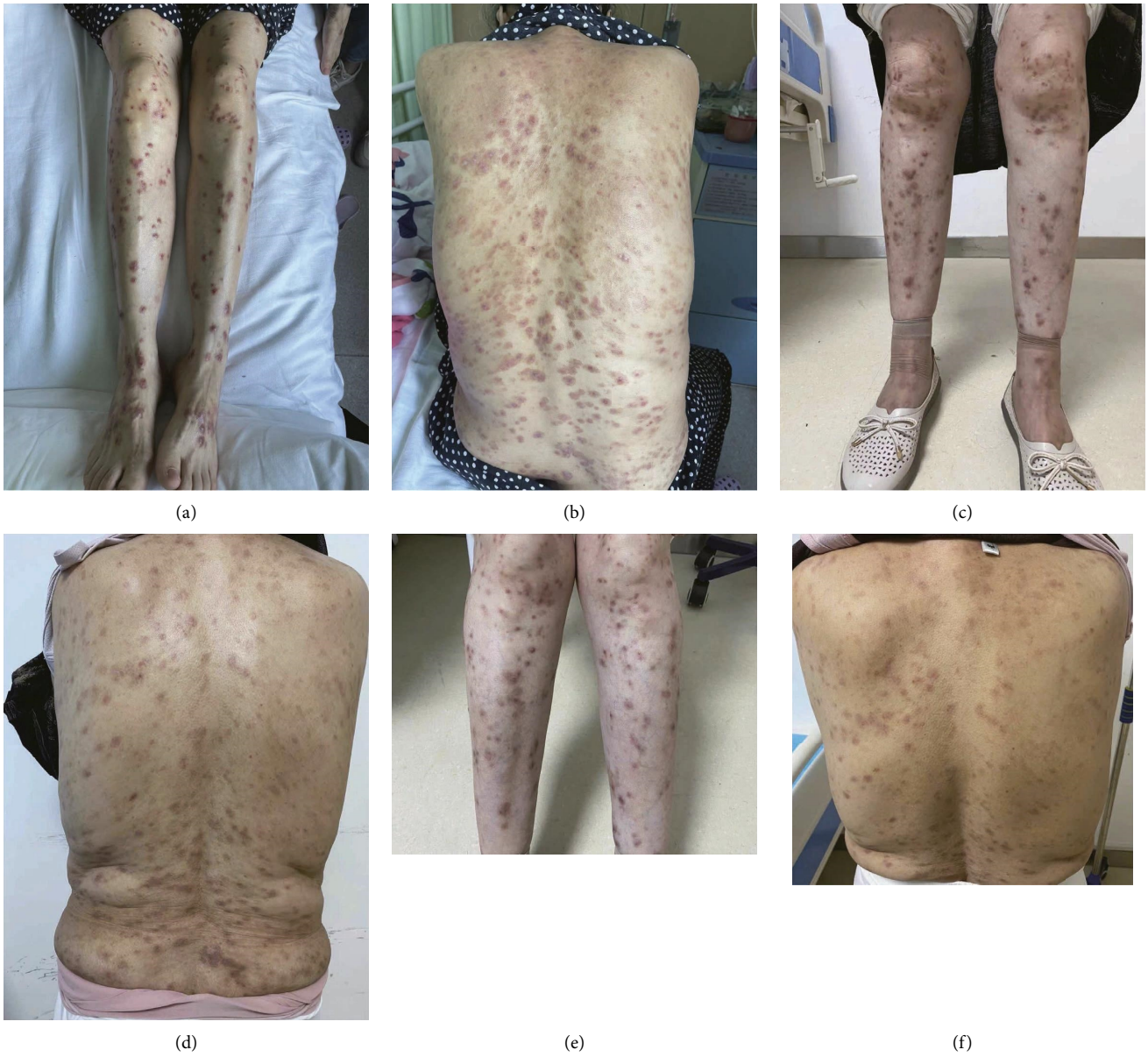

Figure 2: Cutaneous lesions before and after dupilumab treatment. (a, b) are the photos before treatment; (c, d) are the photos after 6 injections of dupilumab; (e, f) are the photos after 10 injections of dupilumab.

treatment, the nodules subsided more slowly, and the remaining skin pigmentation was difficult to subside. At the same time, in our study, there were two patients (6.90%) relapsed after stopping treatment, and both patients had a history of eczema. Therefore, we suggest that PN associated with AD required more weeks of treatment than those with PN associated with non-AD [28]. This finding is consistent with the conclusions of previous studies [28]. Therefore, in the absence of standard therapy, dupilumab appears to be a safe and effective treatment for refractory PN.

In our study, there were two patients who had aggravated primary disease after vaccination. The patients did not take further measures and continued treatment according to the original plan, and then their condition gradually improved. Many adverse effects of vaccination have been reported in other studies. The most common adverse reactions after COVID-19 vaccines are erythema, swelling, tenderness, pain, induration, and itching at the injection site, as well as delayed local reactions, urticaria, and measles-like rash [29]. Certain pre-existing chronic inflammatory skin diseases, such as lupus erythematosus, are induced and aggravated after vaccination against COVID-19 [30]. In addition, many other rare side effects have been reported, such as varicella-zoster virus reactivation, [31] inducing the recurrence of alopecia areata [32]. With the continuous emergence of novel coronavirus variants, the ability of the virus to spread and cause disease has gradually increased. The COVID-19 vaccine remains an effective way to control the spread of the virus and block the epidemic. At present, we can recommend that patients follow the advice of specialists to be vaccinated,

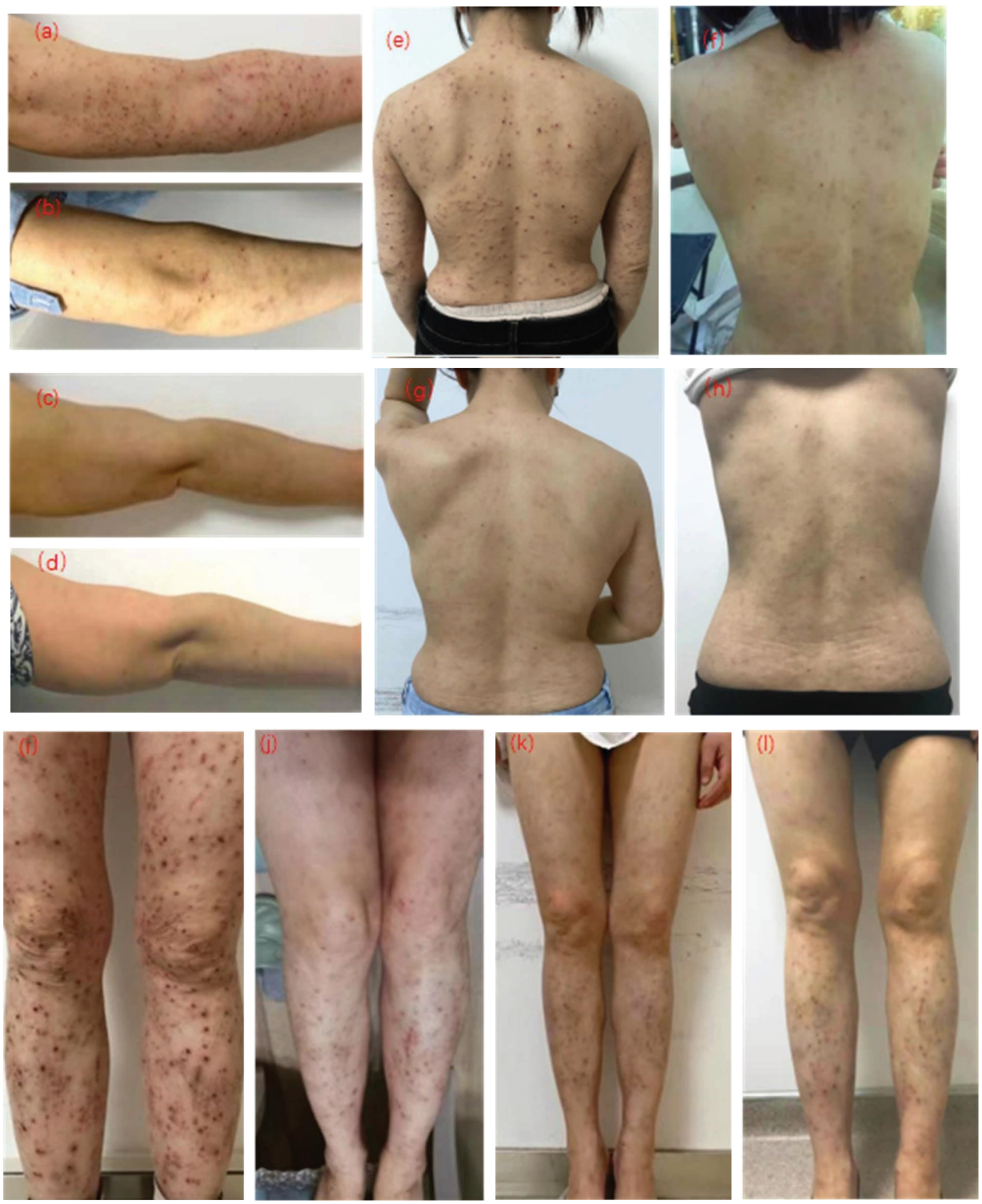

Figure 3: Cutaneous lesions before and after dupilumab treatment. (a, e, i) are photos before treatment, (b, f, j) are photos after 5 injections of dupilumab, (c, g, k) are photos after 7 injections of dupilumab, and (d, h, l) are photos after 10 injections of dupilumab.

pay close attention to the changes after the injection, and provide further treatment if necessary.

This study had certain limitations. First, the sample size was small, and only one hospital was selected for observation. In the future, multiple centers should be combined to carry out retrospective studies to increase the sample size and reduce selection bias. Second, there are some laboratory data because the follow-up method is mainly by telephone, and the laboratory tests of some patients in the later stage of treatment are not carried out in our center, so specific

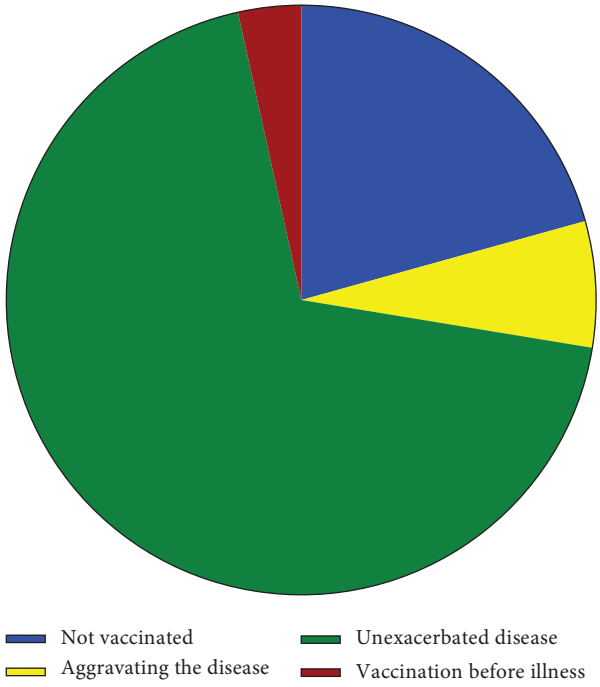

Figure 4: The vaccination status of patients with COVID-19 vaccine.

information cannot be provided. Third, this is a retrospective study, in the future, a long follow-up time and a multicenter prospective cohort study should be conducted to observe the effect of dupilumab. Fourth, this study used the DLQI and NRS scores to evaluate the efficacy, and subjective factors had a greater influence. Therefore, a more objective approach should be sought to assess the efficacy of dupilumab in PN.

5. Conclusion

Our study is a real word study to evaluate the efficacy and safety of the use of dupilumab in patients with PN, and we show that dupilumab appears to be a safe and effective treatment for patients with refractory PN. During the COVID-19 pandemic, we can recommend that patients followed the advice of specialists to be vaccinated during the stable period of the disease, separated from dupilumab treatment one week, paid close attention to the changes in the patient's condition after the injection, and provided further treatment if necessary.

Data Availability

The data used to support the findings of this study are included within the article; further inquiries can be directed to the corresponding author upon request.

Ethical Approval

This study was approved by the appropriate ethics review board of Xi'an Jiao Tong University Second Affiliated Hospital and was in accordance with the Helsinki Declaration. All patients in this study have given written informed consent for publication for all clinical images and health information.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xiaoli Li conceptualized and supervised the study. Wenwen Jing proposed the methodology, investigated the study, and wrote and drafted the original article. Danyang Yang wrote, reviewed, and edited the article. Xin Liu performed the formal analysis. Li Li provided the resources. Tao Lu visualized the study. All authors have seen and approved the final version for publication.

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