Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Case Report

Long-Term Efficacy of Dupilumab for the Treatment of Prurigo Nodularis: A Case Series

Edward M Klepper[1,2*], Maria L Andrzejewski[1,2], Amy Rizkallah[1,2], Jonathan J Lee[3], Howard N Robinson[1,2,4]

[1]Robinson and Max Dermatology PA, Lutherville-Timonium, Maryland, USA

[2]Bernstein and Robinson Dermatology PA, Bel Air, Maryland, USA

[3]Bethesda Dermatopathology Laboratory, Silver Spring, Maryland, USA

[4]The Johns Hopkins Hospital, Baltimore, Maryland, USA

***Correspondence author:** Edward M Klepper, MS, Robinson and Max Dermatology, PA, 101 West Ridgely Road Suite 4B, Lutherville, Maryland, USA, 21093; Email: edwardklepper@gmail.com

Citation: Klepper EM, et al. Long-Term Efficacy of Dupilumab for the Treatment of Prurigo Nodularis: A Case Series. J Dermatol Res. 2023;4(3):1-6.

https://doi.org/10.46889/JDR.2023.4305

Received Date: 01-10-2023

Accepted Date: 20-10-2023

Published Date: 27-10-2023

Abstract

Prurigo nodularis is a chronic, pruritic dermatologic condition that results in nodule formation on the skin that is often treatment refractory and can impair quality of life. The underlying biological mechanism of prurigo nodularis formation is not completely understood, however, many affected patients have an underlying atopic diathesis. Existing therapies provide inadequate outcomes. Dupilumab has recently been approved for the treatment of prurigo nodularis, however, long term efficacy beyond one year has yet to be established. Here we present a series of four patients with prurigo nodularis that were successfully treated with dupilumab and maintained efficacy with a range of 26 months to 79 months.

Keywords: Prurigo Nodularis; Atopic Dermatitis; Atopy; Dupilumab, Interleukin-4; Interleukin-13; Eosinophils; Pruritus

Introduction

Prurigo Nodularis (PN) is a chronic dermatologic condition that results in the formation of multiple pruritic, hyperkeratotic nodules [1,2]. The presentation of PN varies, but generally it appears as flesh-colored, erythematous, hyperpigmented and lichenified papules, plaques, or nodules on the trunk and extensor surfaces of the extremities [1]. Symptoms can be debilitating and severely impact quality of life, more so than almost any other pruritic condition [3]. The pathophysiology of PN is poorly understood but is highly associated with an atopic diathesis [4]. Some studies have suggested that PN is due to altered neuronal signaling that is driven by Interleukin-4 (IL4) and Interleukin-13 (IL13) [5,6]. Dupilumab is a human monoclonal antibody that inhibits the IL4 and IL13 pathways by inhibiting the alpha subunit of the IL4 receptor [7]. Dupilumab has demonstrated success in treating atopic dermatitis and is safe in those as young as six-years-old [8]. While the exact mechanism of action of dupilumab in PN is unknown, several studies have demonstrated that dupilumab is efficacious in reducing pruritus and reduction of lesions caused by the disease [9-20]. Recently, dupilumab has been approved for the treatment of prurigo nodularis, however, efficacy beyond one year has not been established. Here we present a case series of four patients with PN and an underlying atopic diathesis that were successfully treated with dupilumab and maintained efficacy ranging from 26 to 79 months (6.5 years). Dupilumab was chosen due to failure of standard therapies, safety of dupilumab, documented success and the impact on quality of life.

Case Synopsis

Case 1

A 75-year-old male presented with multiple pruritic and erythematous papules and plaques on his trunk, arms and legs. Three-millimeter punch biopsies were obtained from the right and left upper arm for Hematoxylin and Eosin stain (H&E) and Direct

Immunofluorescence (DIF) to rule out eczema versus Bullous Pemphigoid (BP) which showed spongiotic and interface dermatitis suggestive of a drug eruption. The patient was instructed to see his endocrinologist to stop his newest drug, sitagliptin. The patient did not improve after cessation of the drug, therefore, hydrochlorothiazide was stopped and subsequently losartan. The eruption did not improve after stopping the suspected drugs and treatment with triamcinolone 0.1% ointment twice a day for no more than two weeks out of the month, fexofenadine 180 mg daily, emollients twice a day and sarna lotion. Patient was seen six months later with worsening of pruritus and 50% Body Surface Area (BSA) involvement, therefore; biopsies for H&E from the right posterior neck and the right upper back were taken. The patient was considering retirement because the pruritus was so disruptive to his work. The pathology report was consistent with prurigo nodularis. After an informed discussion of risks and benefits, the patient was started on dupilumab two doses of 300 mg/2 ml subcutaneously for loading and then 300 mg/2 ml subcutaneously every other week. The patient was seen three months after treatment and the patient had 95% clearance in prurigo lesions and pruritus. The patient reported significant improvement after only one month of treatment. The back and arms had few 0.5 to 0.8 cm erythematous papules. Six months after starting on dupilumab, the patient had 100% clearance of pruritus and prurigo nodules with remaining post-inflammatory hyperpigmentation. The patient maintains 100% clearance of prurigo lesions, eczema and pruritus to this day and continues to have improved quality of life after 74 months of uninterrupted therapy and without side effects.

Case 2

A 54-year-old female with a history of seasonal allergies initially presented with numerous excoriated pink papules on her trunk, arms and legs. Biopsies for H&E and DIF were taken from the right back and right posterior shoulder. The pathology report showed spongiotic dermatitis with eosinophils suggestive of a dermal hypersensitivity reaction or eczematous process. She was started on fexofenadine 180 mg one tab daily, hydroxyzine 50 mg one tab every night, Aveeno body wash, tacrolimus 0.1% ointment daily, betamethasone 0.05% ointment once a day as needed for break through itch and Cerave moisturizing lotion twice a day. One month later, the patient presented for follow-up with progression to 80% BSA involvement of excoriated, lichenified erythematous papules and plaques on her arms, legs, abdomen, chest, buttocks and hands, which were clinically consistent with development of and/or progression towards prurigo nodularis. After an informed discussion of risks and benefits, the patient was started on dupilumab two doses of 300 mg/2 ml subcutaneously for loading and then 300 mg/2 ml subcutaneous injection every other week. The patient stopped all topicals with the exception of a moisturizer and cetirizine 10 mg daily for her seasonal allergies. An additional biopsy to confirm the development of PN was not performed due to the clinical presentation of progressing, enlarging, pruritic, plaques in reachable areas and the need to rapidly initiate treatment for worsening symptoms. She had 80% BSA involvement at the one month follow up and 4% BSA at her three month follow up with significant reduction in pruritus and erythematous papules and plaques. Treatment is ongoing and this efficacy has been maintained for a total duration of 33 months and without adverse events.

Case 3

A 66-year-old male patient with a history of recalcitrant atopic dermatitis with overlap of prurigo nodularis presented with multiple superficial erosions and excoriations with hyperpigmented, lichenified papules and plaques on the arms and legs almost appearing as a factitial dermatitis. Patient was previously seen by multiple dermatologists prior to presenting and biopsy results showed spongiotic dermatitis and lichen simplex chronicus. The intensity of pruritus was 10/10 to the point where the patient could not function other than repeatedly excoriating his extremities. The patient started phototherapy in 2009, with some improvement, however, after cessation of phototherapy, PN resurfaced. Other treatments the patient received included intralesional injections of triamcinolone 5-10 mg/mL monthly and 40 mg/mL intramuscular triamcinolone injections. Intralesional injections developed secondary infections, which were treated with topical mupirocin 2% ointment. The patient was recommended to try bleach baths, but was unable to tolerate them. At the time of anticipating the use of dupilumab, the patient progressed to 40% BSA involvement on the trunk, upper and lower extremities and developed erythematous plaques with excoriations consistent with intractable atopic dermatitis with lichen simplex chronicus and PN. At that time, the patient's insurance denied coverage. One month following, PN progressed to 70% BSA, with erythematous patches with scales, excoriations, hyperpigmentation, some superficial erosions and hyperkeratotic papules and plaques. The patient was again denied coverage for dupilumab. One month later, the disease progressed to 90% BSA. Additional biopsies were not performed to confirm diagnosis of PN as the previous biopsies showed progression from spongiotic dermatitis to lichen simplex chronicus along with the classic clinical progression to PN as demonstrated by the development and proliferation of erythematous,

hyperpigmented plaques on reachable areas. In February of 2017, after an informed discussion of risks and benefits, the patient was started on dupilumab two doses of 300 mg/2 ml subcutaneously for loading and then 300 mg/2 ml subcutaneous injection every other week. The patient additionally was using topical triamcinolone 0.1% ointment as needed and emollients and mupirocin 2% ointment for infected sites. One month after treatment, the patient had 60% improvement on the back and upper arms and 20-30% improvement on the lower extremities. The patient reported that he was "itching very little" and feeling like his "skin is more resistant". Two months after initiating treatment, the patient presented with faded erythematous macules and atrophic patches on the back, arms and thighs. The patient no longer required triamcinolone or mupirocin, but was using emollients. Six months after initiating treatment, the patient presented with an occasional mild itch on the back. On exam, the patient only had slightly hyperpigmented patches on the back, trunk and extremities, with only 2% BSA involvement. After nine months of treatment, the patient presented for follow up. On exam, the patient had less than 2% BSA involvement with erythematous macules and papules present. After one full year of treatment, his legs, arms and trunk were clear. Currently, the patient is still on dupilumab and maintains less than 2% BSA involvement without pruritus after 79 months of uninterrupted therapy and without side effects.

Case 4

A 56-year-old male with a history of atopic dermatitis presented with erythematous patches with scale affecting his trunk, arms and legs with approximately 20% BSA involvement. Patient was using crisaborole 2% ointment twice a day, triamcinolone 0.1% ointment twice a day for two weeks out of every month and emollients without improvement. Dupilumab was considered but denied by insurance. Tacrolimus 0.1% ointment twice a day for two weeks then three times per week was started. Patient worsened and developed multiple erythematous papules with scale on the bilateral forearms, bilateral flanks, abdomen and hands with now 25% BSA (Fig. 1). A punch biopsy was obtained which showed traumatized PN (Fig. 2). After an informed discussion of risks and benefits, the patient was started on dupilumab two doses of 300 mg/2 ml subcutaneously for loading dose and then 300 mg/2 ml subcutaneous injection every other week. After three months of treatment, the patient presented for follow-up and he had almost 100% clearance and a BSA of less than one percent. He had faded erythematous macules on the right and left forearms (Fig. 3). This improvement has been maintained after 26 months of uninterrupted therapy with dupilumab and without side effects.

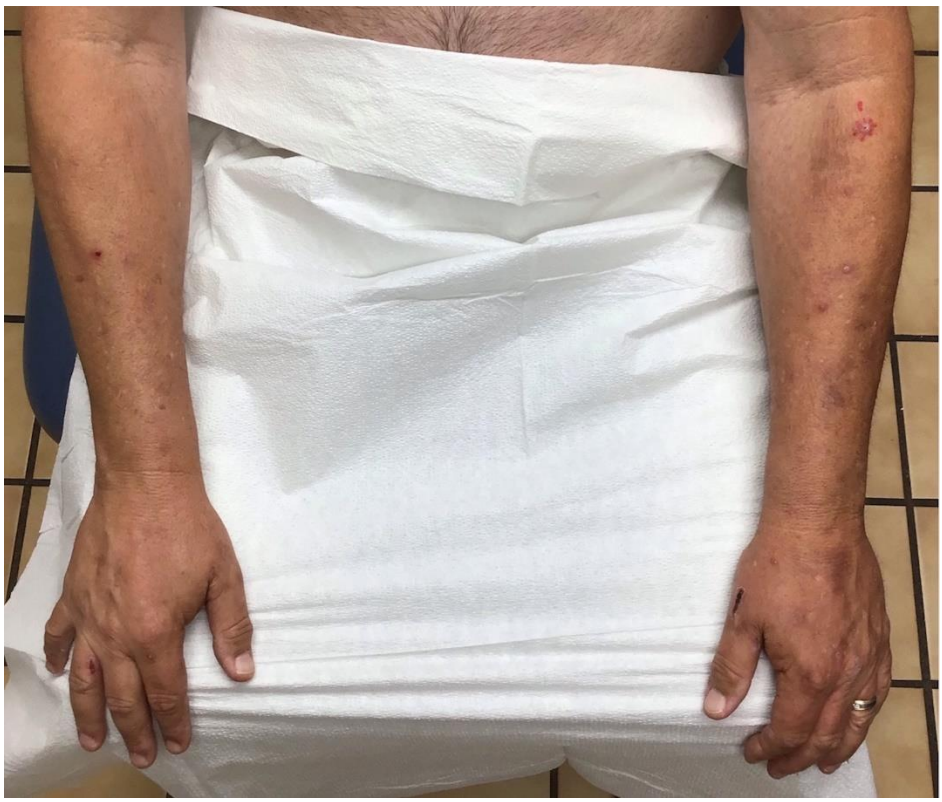

Figure 1: Multiple erythematous papules with scale on bilateral forearms and hands.

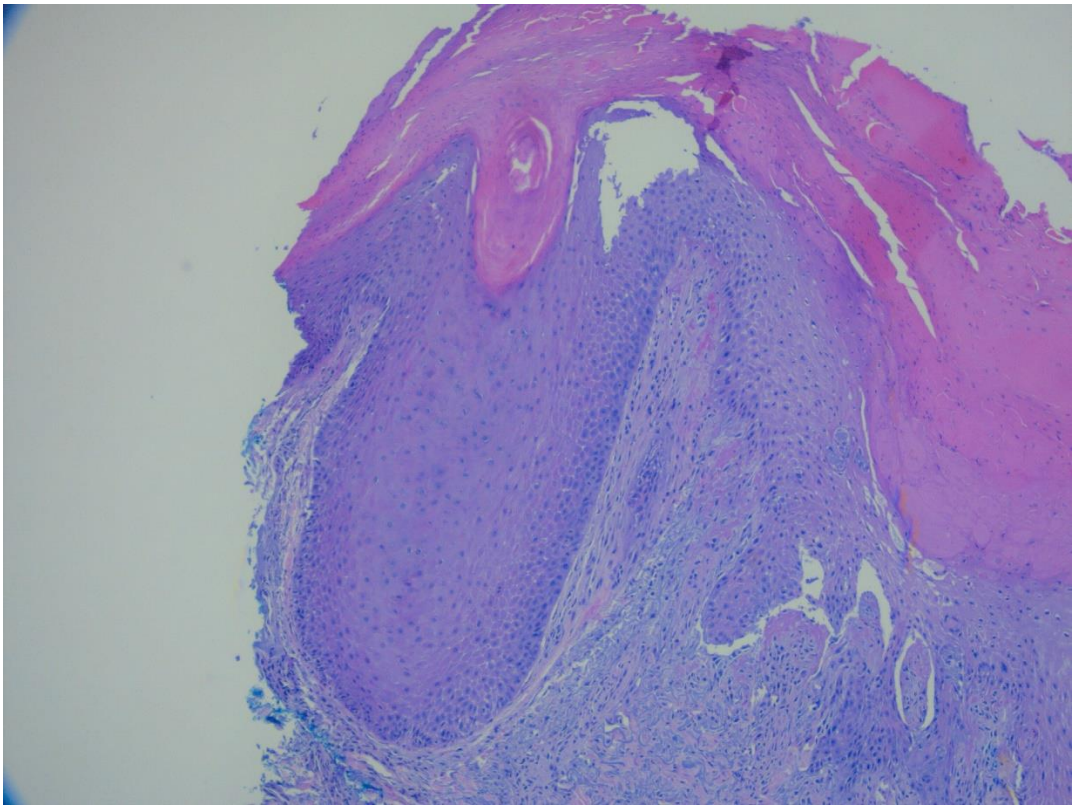

Figure 2: H&E histopathology shows prurigo nodularis with trauma. There are hyperkeratosis, epidermal and adnexal epithelial hyperplasia and dilation, with thickening of the papillary dermis by coarse collagen bundles arranged in vertical streaks. There is epidermal devitalization, impetiginized scale and subepidermal fibrin, suggestive of trauma, 20x.

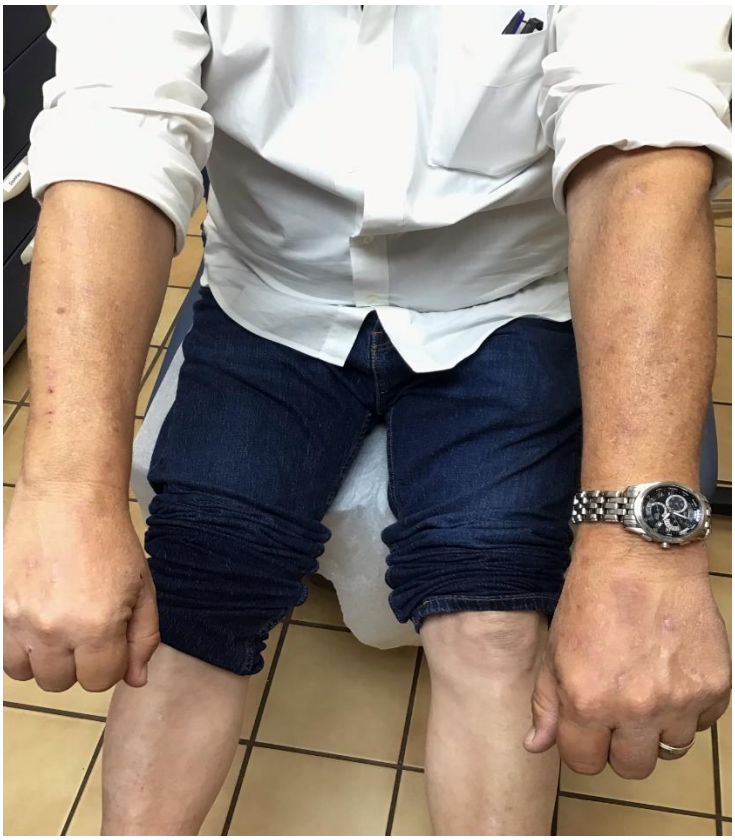

Figure 3: After treatment, the patient presented with faded erythematous macules on the right and left forearms.

Case Discussion

Dupilumab is a fully human monoclonal Immunoglobulin G4 (IgG4) antibody that targets Interleukin-4 receptor alpha (IL-4ra). Binding results in the decreased signaling of T-helper 2 cytokines, IL4 and IL13. It has been recently approved by the FDA for the treatment of prurigo nodularis. It is also approved for moderate-to-severe asthma ages 12 and older, moderate-to-severe atopic dermatitis ages 6 and older and inadequately controlled rhinosinusitis with nasal polyposis ages 18 and older [7]. The indications that dupilumab are approved for are characterized by the type-2 inflammatory response and production of eosinophils [21]. Both cytokines that dupilumab target drive the activation of B-cells, chemotaxis of eosinophils and class switching of B-cells in atopic dermatitis [22,23]. The underlying pathophysiology of PN is currently unknown. However, the type 2 inflammatory pathway is thought to contribute as evidenced by the presence of Signal Transducer and Activator Of Transcription 6 (STAT 6), a marker for interleukin-4, interleukin-5 and interleukin-13, in skin biopsies of patients with PN. Chronic pruritus is thought to be driven by neuronal signaling from IL-4 and IL-13 [5,6]. This neuronal signaling is initiated by an allergen or pruritogen stimulating a cascade of events thought to be triggering an almost infinite feedback loop that contributes to the pruritus and then development of PN [24]. The granular components of eosinophils have also been identified in increased numbers surrounding nerve fibers in prurigo lesions. Their presence suggests eosinophils are possibly involved in the pathogenesis of PN [25]. The presence of STAT 6 and granular components of eosinophils in prurigo skin suggests a possible target for the treatment of PN. Currently, dupilumab is the only FDA approved treatment for PN [7]. Many other treatments are attempted often without adequate relief. Treatments for this debilitating, pruritic disease have included corticosteroids, phototherapy, antihistamines, emollients, neuromodulators, intralesional triamcinolone and immunosuppressants [2]. Some of these treatments can come with significant side effects, especially for the geriatric population [2]. The safety profile with dupilumab is unparalleled when compared to other systemic therapies or biologics, including blockade of the janus kinase/STAT pathway, as evidenced by its use in pediatrics ages 6 and older [7,26,27]. The patients in our study had an underlying atopic diathesis. The association of underlying atopy with PN has been well documented [2]. It is possible that dupilumab was effective because prurigo nodularis was the clinical manifestation of underlying atopy. All cases had improvement by three months of therapy and improvement was maintained with a range of 26 months and the longest treated patient of six and a half years (79 months) at the time of this writing. Patients varied in concomitant therapy and no one needed to stop treatment due to side effects. The results of this case series are suggestive of the long-term efficacy of dupilumab for the treatment of PN.

Limitations of Study

Limitations of this case series include small sample size, lack of standardized measuring tools and adjuvant therapy of topical steroids, antihistamines and emollients. Further research is needed on the safety, efficacy, dosing and duration of therapy for those with PN. The effectiveness of dupilumab for PN in those with and without a history of atopy needs to be evaluated as well [7].

Conclusion

We report an additional four cases in which prurigo nodularis has been successfully treated with dupilumab. We anticipate that dupilumab's lack of immune suppression and low side effect profile could make it another therapy option for those with intolerance to traditional therapies or limitations. This case series contributes to the growing body of evidence of the effectiveness of dupilumab for the treatment of PN. It further supports the efficacy of dupilumab for the treatment of prurigo nodularis.

Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Huang AH, Williams KA, Kwatra SG. Prurigo nodularis: epidemiology and clinical features. J Am Acad Dermatol. 2020;83:1559-65.
2. Zeidler C, Yosipovitch G, Ständer S. Prurigo nodularis and its management. Dermatol Clin. 2018;36:189-97.
3. Janmohamed SR, Gwillim EC, Yousaf M, Patel KR, Silverberg JI. The impact of prurigo nodularis on quality of life: a systematic review and meta-analysis. Arch Dermatol Res. 2021;313:669-77.
4. Iking A, Grundmann S, Chatzigeorgakidis E. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. J Eur Acad Dermatol Venereol. 2013;27:550-7.
5. Fukushi S, Yamasaki K, Aiba S. Nuclear localization of activated STAT6 and STAT3 in epidermis of prurigo nodularis. Br J Dermatol.

2011;165:990-6.
6. Oetjen LK, Mack MR, Feng J. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. Cell. 2017;171:217-28.
7. US FDA. Dupixent® (dupilumab) injection, for subcutaneous use: us prescribing information; 2022. [Last accessed on: October 20, 2023] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761055s044lbl.pdf
8. Olesen CM, Holm JG, Nørreslet LB. Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral centre. J Eur Acad Dermatol Venereol. 2019;33:1562-8.
9. Beck KM, Yang EJ, Sekhon S, Bhutani T, Liao W. Dupilumab treatment for generalized prurigo nodularis. JAMA Dermatol. 2019;155:118-20.
10. Chiricozzi A, Maurelli M, Gori N. Dupilumab improves clinical manifestations, symptoms and quality of life in adult patients with chronic nodular prurigo. J Am Acad Dermatol. 2020;83:39-45.
11. Georgakopoulos JR, Croitoru D, Felfeli. Long-term dupilumab treatment for chronic refractory generalized prurigo nodularis: A retrospective cohort study. J Am Acad Dermatol. 202;85:1049-51.
12. Giura MT, Viola R, Fierro MT, Ribero S, Ortoncelli M. Efficacy of dupilumab in prurigo nodularis in elderly patient. Dermatol Ther. 2020;33:1-3.
13. Holm JG, Agner T, Sand C, Thomsen SF. Dupilumab for prurigo nodularis: Case series and review of the literature. Dermatol Ther. 2020;33:1-6.
14. Kovács B, Rose E, Kuznik N. Dupilumab for treatment-refractory prurigo nodularis. J Dtsch Dermatol Ges. 2020;18:618-24.
15. Liu T, Bai J, Wang S. Effectiveness of dupilumab for an elderly patient with prurigo nodularis who was refractory and contradicted to traditional therapy. J Asthma Allergy. 2021;14:175-8.
16. Mollanazar NK, Elgash M, Weaver L, Valdes-Rodriguez R, Hsu S. Reduced itch associated with dupilumab treatment in 4 patients with prurigo nodularis. JAMA Dermatol. 201;155:121-2.
17. Napolitano M, Fabbrocini G, Scalvenzi M. Effectiveness of dupilumab for the treatment of generalized prurigo nodularis phenotype of adult atopic dermatitis. Dermatitis. 2020;3:81-4.
18. Rambhia PH, Levitt JO. Recalcitrant prurigo nodularis treated successfully with dupilumab. JAAD Case Rep. 2019;5:471-3.
19. Romano C. Safety and effectiveness of dupilumab in prurigo nodularis. J Investig Allergol Clin Immunol. 2021;31:162-3.
20. Russo F, Provvidenziale L, Bruzziches F. Psoriasis-like eruption triggered by dupilumab therapy. Dermatitis. 2021;32:1-2.
21. Seidman JS, Eichenfield DZ, Orme CM. Dupilumab for bullous pemphigoid with intractable pruritus. Derm Online J. 2019;25:1-5.
22. Braddock M, Hanania NA, Sharafkhaneh A, Colice G, Carlsson M. Potential risks related to modulating interleukin-13 and interleukin-4 signaling: A systematic review. Drug Saf. 2018;41:489-509.
23. Hamilton JD, Suárez-Fariñas M, Dhingra N. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2014;134:1293-300.
24. Yosipovitch G, Berger T, Fassett MS. Neuroimmune interactions in chronic itch of atopic dermatitis. J Eur Acad Dermatol Venereol. 2020;34:239-50.
25. Johansson O, Liang Y, Marcusson JA, Reimert CM. Eosinophil cationic protein- and eosinophil-derived neurotoxin/eosinophil protein X-immunoreactive eosinophils in prurigo nodularis. Arch Dermatol Res. 2000;292:371-8.
26. Damsky W, King BA. JAK inhibitors in dermatology: The promise of a new drug class. J Am Acad Dermatol. 2017;76:736-44.
27. Rajasimhan S, Pamuk O, Katz JD. Safety of janus kinase inhibitors in older patients: A focus on the thromboembolic risk. Drugs Aging. 2020;37:551-8.