doi:10.36849/JDD.8060

Improvement of Hailey-Hailey Disease Following Administration of Dupilumab

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ABSTRACT

Hailey-Hailey disease (HHD) is a rare, chronic skin disorder characterized by recurrent inflammatory plaques with painful blisters, erosions, and macerations. We report a case of a 40-year-old female with clinical and pathological findings consistent with HHD. After numerous unsuccessful treatments, including the use of antiseptic washes, topical and oral medications, and injections, the patient was started on dupilumab (300 mg/2 mL syringes every 2 weeks). After 4 months of treatment, there was a clearance of plaques and resolution of pain with only minimal residual erythema. This response was maintained with no reported side effects. Dupilumab may be an effective and safe treatment option for refractory HHD, but it necessitates further research.

J Drugs Dermatol. 2025;24(4):410-412. doi:10.36849/JDD.8060

INTRODUCTION

Hailey-Hailey disease (HHD), also called benign familial pemphigus or benign chronic pemphigus, is a rare, autosomal dominant disorder that affects the adhesion of epidermal keratinocytes. This chronic, relapsing condition is characterized by recurrent painful blistering, erosions, maceration, and frequent secondary infections in the intertriginous and flexural areas. HHD is caused by loss-of-function variants in the ATP2C1 gene at 3q22.1, which encodes the ATP-powered, magnesium-dependent calcium pump protein hSPCA1. Its function is to maintain normal intracellular concentrations of free calcium by sequestering calcium into the Golgi apparatus.[1] While the precise mechanism is not completely understood, the genetic defect causes high cytosolic calcium levels, resulting in altered cellular connections within the epidermis. HHD can also be exacerbated by trauma, friction, sweat, and secondary infections. Although rare, HHD is a chronic and painful condition that can impact a patient's physical and psychological well-being.

Currently, there is no cure for the disease. The mainstay of existing treatments focuses on the management of the disease and avoidance of moisture, which is largely based on case reports and small observational studies. Topical therapies are considered first-line for mild manifestations of the disease and include topical antibiotics, antifungals, corticosteroids, and calcineurin inhibitors.[2] Patients with severe disease manifestations have shown improvement with the addition of systemic treatments such as oral antibiotics and/or intralesional botulinum toxin injections.[3] Last-line treatments include surgical excision, ablation, or radiation therapy.[4]

Dupilumab, or Dupixent, is a human monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling and has been approved for use in conditions such as atopic dermatitis, asthma, and prurigo nodularis. Dupilumab has shown long-term safety and efficacy in treating atopic dermatitis. This drug has a favorable safety profile with the most common adverse events including nasopharyngitis, conjunctivitis, and injection-site reactions.[5] This report documents a case of successful treatment of refractory Hailey-Hailey disease with dupilumab.

CASE REPORT

A 40-year-old female with a past medical history of hypothyroidism and atopic dermatitis presented to the clinic with a chief complaint of recurrent skin lesions and erosions to the bilateral axilla for four years. The patient reported intermittent burning and soreness associated with the rash. She also had a history of methicillin-resistant Staphylococcus aureus (MRSA) skin infections in the areas, which were treated with Bactrim courses by her primary care physician. The patient denied a family history of blistering cutaneous disease.

On physical exam, there were well-defined, erythematous, scaly papules and plaques with linear erosions and yellow crusting in the bilateral axillary vaults (Figure 1). A biopsy of the right axilla demonstrated full-thickness suprabasilar acantholysis

FIGURE 1. Erythematous, scaly papules and plaques with linear erosions on bilateral axillae prior to dupilumab treatment.

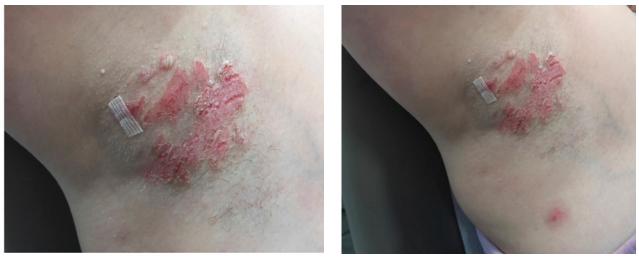
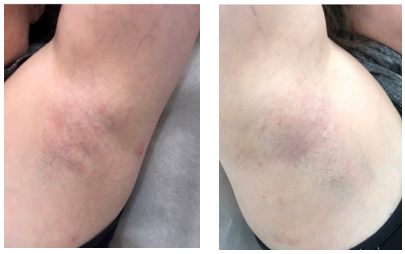


FIGURE 2. Clearance of plaques with only minimal residual erythema after 4 months of dupilumab treatment.



with overlying hyperkeratosis, consistent with Hailey-Hailey disease. The patient tried numerous treatments without clinical improvement, including antiseptic washes, topical tacrolimus ointment, topical and intralesional steroids, oral antifungals, oral antibiotics, glycopyrrolate, naltrexone, and botulinum toxin injections. The patient later began to develop papules and plaques in the groin and inframammary folds. After many failed therapies, the treatment team and patient decided to trial dupilumab (300 mg/2 mL syringes every 2 weeks). Within 4 months of beginning dupilumab, the patient had clearance of plaques with only minimal residual erythema left to bilateral axillae (Figure 2). The patient also reported resolution of pain and significant improvement in quality of life. This response was maintained with no reported side effects.

DISCUSSION

Our patient with HHD, supported by clinical and biopsy findings, was successfully treated with dupilumab. Lesions were cleared with only minimal residual erythema after 4 months of treatment and no notable side effects.

There have been many recent reports using dupilumab off-label to successfully treat a wide range of inflammatory cutaneous diseases, including bullous pemphigoid, acquired perforating dermatosis, palmoplantar pustulosis, and HHD. One case series

TABLE 1.

Response After Administration of Dupilumab in Hailey-Hailey Disease

Author (Year) PMID	Age (Years)/ Gender	Duration of Symptoms Prior to Dupilumab Treatment (Years)	Previous Treatments	Outcome of Dupilumab Course	Concomitant Treatments
Alzahrani et al[6] (2021) PMID: 33971025	50s/F	20+	A, Abx, AH, CLI, CLOT, CsA, E, I, LDN, Pred, SS, TCS, 5FU, and various OTC supplements	Significant improvement after an average of 2 months; improvement sustained at 21 months follow-up	None
Alzahrani et al[6] (2021) PMID: 33971025	50s/M	5	A, GLY, LDN, TCS	Significant improvement after an average of 2 months; improvement sustained at 25 months follow-up	Betamethasone valerate cream
Alzahrani et al[6] (2021) PMID: 33971025	70s/M	33	BTX, ILS, and numberous unspecified topical therapies	Significant improvement after an average of 2 months; improvement sustained at 17 months follow-up	Topical desonide lotion and antiperspirant
Alamon-Reig et al[7] (2022) PMID: 35734956	56/F	10	A, AH, AP, CsA, D, DS, Fluc, HCQ, LDN, Min, MTX, Ox, Pred, S, TCS, TT	Significant improvement after 2 months of treatment	Topical clobetasol propionate ointment
Alamon-Reig et al[7] (2022) PMID: 35734956	52/M	12	A, AP, CO2 laser, D, LDN, Min, MMp, Ox, Pred, TCS	No improvement reported	Topical fusidic acid, hydrocortisone ointment and Ox 5 mg/day
Alamon-Reig et al[7] (2022) PMID: 35734956	59/M	25	A, AH, AP, DS, LDN, Min, Pred, TCS	Significant improvement after 5 months of treatment	Antihistamine as needed
Present Case	40/F	4	Abx, AW, BTX, GLY, ILS, LDN, OAF, TCS, TT	Clearance of plaques with only minimal residual erythema after 4 months of treatment	None

A, acitretin; Abx, oral antibiotics; AH, antihistamines; AP, apremilast; AW, antiseptic washes; BTX, botulinum toxin injections; CLI, topical clindamycin; CLOT, clotrimazole; CO2 laser, carbon dioxide laser; CsA, cyclosporine; D, doxycycline; DS, dapsone; E, etanercept; F, female; Fluc, fluconazole; GLY, glycopyrrolate; HCQ, hydroxychloroquine; I, isotretinoin; ILS, intralesional steroids; LDN, low-dose naltrexone; M, Male; Min, Minocycline; MMp, mofetil mycophenolate; MTX, methotrexate; OAF, oral antifungals; OTC, over-the-counter; Ox, oxybutynin; Pred, prednisone; S, sulfone; SS, silver sulfadiazine; TCS, topical corticosteroids; TT, topical tacrolimus; 5FU, topical fluorouracil.

of 3 patients with recalcitrant HHD showed significant clinical response to treatment with dupilumab.[6] Another case series described lower response rates in the use of dupilumab in three patients with HHD, with only two patients maintaining significant clinical improvement.[7] These 2 case studies are limited by the number of participants and the lack of a universal assessment scale for this disease. This is only the 7th known case, to the best of our knowledge, of recalcitrant HHD treated with dupilumab that has been reported in the literature (Table 1). This case highlights a potentially exciting new alternative therapy for patients with refractory moderate to severe Hailey-Hailey disease, necessitating further research.

CONCLUSION

Our patient with Hailey-Hailey disease was successfully treated with dupilumab after failing all other current treatments, with a near-complete resolution of lesions and no notable adverse effects. Further studies of IL-4 receptor antagonist use in Hailey-Hailey disease can improve our understanding of the drug's therapeutic potential. Future studies could also examine its use in similar acantholytic diseases, such as Darier disease, to gain a better understanding of the treatment potential and range of dupilumab.

DISCLOSURES

The authors have no conflicts of interest to disclose.

ACKNOWLEDGMENT

We would like to thank the patient for providing permission for this case report.

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