Successful treatment of bullous pemphigoid with dupilumab: a case and brief review of the literature

Maleck Saleh[1] MBA, Matthew Reedy[1,2] MD, Helen Torok[2] MD, Joshua Weaver[1,2] MD

Affiliations: [1]Northeast Ohio Medical University, Rootstown, Ohio, USA, [2]Trillium Creek Dermatology and Surgery Center, Medina, Ohio, USA

Corresponding Author: Matthew Reedy MD, 5783 Wooster Pike, Medina, OH 44256, Tel: 330-221-1297, Email: mattsreedy@gmail.com

Abstract

Bullous pemphigoid is an autoimmune skin disease that results in formation of pruritic blisters. Most cases are treated with a combination of systemic and topical corticosteroids as well as other immunomodulatory drugs. Dupilumab is a fully human monoclonal antibody that acts as an antagonist against IL4Rα traditionally used in the treatment of atopic dermatitis. We present an 80-year-old man with moderate-to-severe bullous pemphigoid successfully treated with dupilumab.

Keywords: bullous pemphigoid, corticosteroid resistant, dupilumab

Introduction

Dupilumab (Dupixent®, Regeneron Pharmaceuticals, Terrytown, NY; Sanofi Genzyme, Cambridge, MA) is a fully human monoclonal antibody that acts as an antagonist against IL4Rα. Because the α-subunit of IL4 is able to dimerize with a subunit of IL13, dupilumab is able to regulate both IL4 and IL13 cytokine signaling [1]. In 2017, The FDA approved its usage for treatment of moderate-to-severe atopic dermatitis in patients whose disease did not respond adequately to topical prescriptions or were unable to undergo topical prescription therapy [1,2]. Dupilumab has recently been implicated as a possible therapeutic option for conditions other than atopic dermatitis including bullous pemphigoid (BP), [3,4]. We present a patient with corticosteroid-resistant BP who demonstrated marked improvement after treatment with dupilumab.

Case Synopsis

An 80-year-old man presented to clinic with a three-month history of pruritic eruptions on the arms, legs, and trunk. He had a previous biopsy that revealed eosinophilic spongiosis (**Figure 1**) that was being treated with topical triamcinolone ointment without notable improvement. Clinically, his disease progressed into pink, smooth urticarial papules and plaques with scattered bullae and erosions on the distal leg and dorsal feet. A biopsy for direct immunofluorescence was performed, which revealed positive linear immunoreactivity for IgG and C3 deposition along the basement membrane zone, confirming the diagnosis of BP. He was started on prednisone 40mg daily, doxycycline 100mg twice daily, and niacinamide 500mg three times per day. Improvement was noted at his two-week follow-up and the decision was made to gradually wean his prednisone dose over the following month. The patient then experienced a significant flare of his

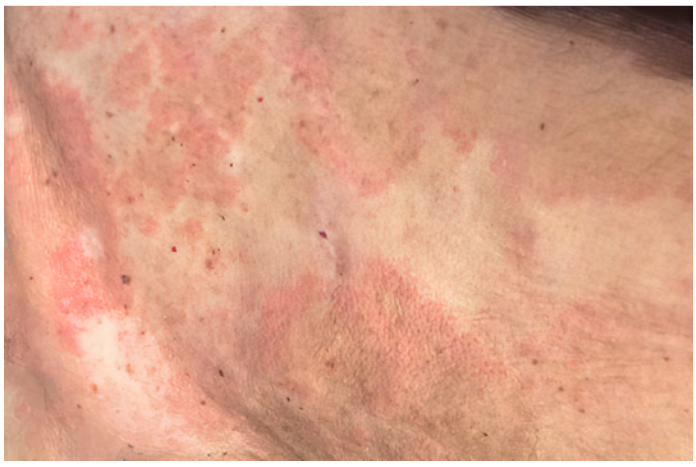

Figure 1. *Erythematous smooth papules and plaques on the trunk.*

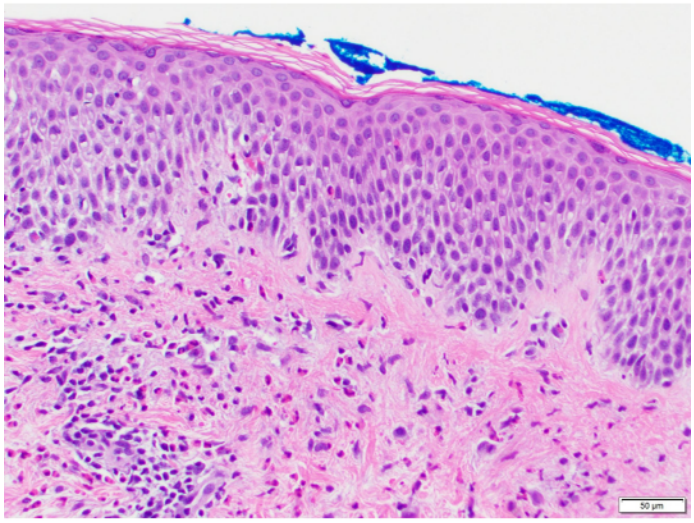

Figure 2. *H&E revealing eosinophilic spongiosis, 200×.*

disease. His prednisone dose was increased back to 40mg daily and he was started on mycophenolate mofetil 500mg twice daily with plans to eventually titrate up to 1,000mg twice daily. The patient elected to discontinue the mycophenolate mofetil after one week of therapy owing to adverse side effects of lethargy, upset stomach, and tremors. His disease continued to flare, displaying similar symptoms seen at his prior visits (**Figure 2**) and the decision was made to trial the patient on dupilumab. Therapy was started with an initial subcutaneous injection of 600mg of dupilumab. The patient returned to clinic two-weeks later with marked improvement (**Figure 3**). Therapy was continued with subcutaneous injection of dupilumab 300mg every two weeks with complete clearance of his disease. The patient's prednisone was tapered off and he is currently controlled on dupilumab and doxycycline with no active skin lesions or pruritus.

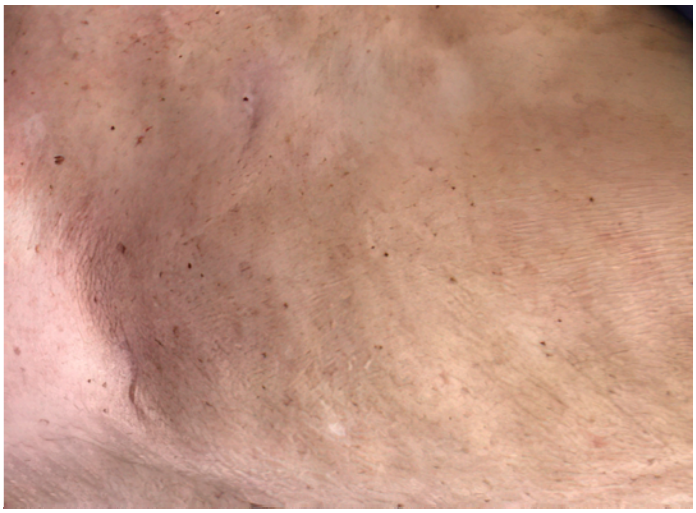

Figure 3. *Lesions nearly resolved with post-inflammatory hyperpigmentation.*

Case Discussion

Bullous pemphigoid is an autoimmune disease characterized by subepidermal blistering and inflammation with a wide range of severity. It is considered to be a Th2-dominant disease with subsequent overexpression of Th2-type cytokines such as IL4, IL5, and IL13 [5,6]. IL4 is specifically associated with the recruitment of eosinophils which contribute to the incessant pruritis present with the disease. Dupilumab may be a viable therapy option for BP owing to its IL4Rα antagonism and additional IL13 inhibitory properties, particularly since itch severity in BP has been correlated with elevations in a number of cytokines including IL13 [1,3,4,7]. In this report, we present a case of corticosteroid-resistant BP being successfully treated with dupilumab after attempting other conventional treatment options. In this particular case, treatment with mycophenolate mofetil was attempted but discontinued because of immediate adverse effects. Dupilumab may serve as a viable treatment option in patients unable to tolerate traditional therapy, especially since the adverse effects associated with dupilumab are relatively mild [8]. Review of the literature revealed fifteen other cases of dupilumab being used in the treatment of BP (**Table 1**). In each case, dupilumab was administered as an initial injection of 600mg followed by 300mg injections every two weeks. The largest cohort came from a recent case series by Abdat et al. [11].

Conclusion

Owing to the relatively small number of patients who have undergone this therapy, further studies are needed to fully assess the efficacy, viability, and practicality of dupilumab for the treatment of BP. The mild side effect profile of dupilumab would make it an ideal option for treating the elderly and patients with co-morbidities, the vast majority of those afflicted with the disease.

Potential conflicts of interest

The authors declare no conflicts of interest.

Table 1. *Cases of bullous pemphigoid treated with dupilumab.*

Publication year [ref]	Therapies failed prior to dupilumab	Outcome of dupilumab therapy
2018 [9]	Prednisone	Pruritis resolved after one week, blisters resolved within one month of treatment, stable after three months
2019 [10]	Doxycycline, nicotinamide, mycophenolate mofetil, prednisone, clobetasol cream, triamcinolone, omalizumab	Pruritis improved after two weeks, blisters resolved after 7 weeks, stable after one year
2020 [11]	Prednisone, not eligible for mycophenolate mofetil treatment due to Hep B and TB positivity	Clearance of disease symptoms
2020 [11]	Prednisone, mycophenolate mofetil, doxycycline, niacinamide	Clearance of disease symptoms
2020 [11]	Prednisolone, methotrexate (patient received weekly methotrexate alongside dupilumab therapy), IVIG	Clearance of disease symptoms
2020 [11]	Doxycycline	Clearance of disease symptoms
2020 [11]	None	Pruritis improved, no clearance of bulla
2020 [11]	Prednisone, methotrexate	Pruritis improved, clearance of bulla after one month of treatment
2020 [11]	Prednisone (patient received taper course alongside dupilumab), doxycycline, niacinamide	Clearance of disease symptoms
2020 [11]	Methotrexate (patient received methotrexate alongside dupilumab)	Clearance of disease symptoms
2020 [11]	Rituximab, IVIG, doxycycline, nicotinamide, azathioprine	No improvement in disease symptoms, dupilumab discontinued after 8 weeks
2020 [11]	Prednisone, mycophenolate, rituximab, IVIG (patient received intralesional steroids and topical steroids alongside dupilumab)	Pruritis improved, clearance of bulla after three months of treatment
2020 [11]	Prednisone, methotrexate (patient received methotrexate weekly alongside dupilumab)	Pruritis did not improve, clearance of bulla after four months of treatment
2020 [11]	Prednisone (patient received a taper course alongside dupilumab)	Clearance of disease symptoms
2020 [11]	Prednisone (patient received a taper course alongside dupilumab)	Pruritis improved, bulla improved, disease symptoms were not fully cleared
2020*	Prednisone, mycophenolate mofetil, niacinamide, doxycycline (patient received doxycycline alongside dupilumab therapy)	Clearance of disease symptoms, currently stable

*denotes the patient presented within this case report.

References

1. Shirley M. Dupilumab: First Global Approval. *Drugs*. 2017;77:1115-1121. [PMID: 29312544].
2. Mullard A. FDA approves dupilumab for severe eczema. *Nat Rev Drug Discov*. 2017;16:305-305. [PMID: 28450716].
3. Hendricks AJ, Yosipovitch G, Shi VY. Dupilumab use in dermatologic conditions beyond atopic dermatitis – a systematic review. *J Dermatol Treat*. 2021;32:19-28. [PMID: 31693426].
4. Maloney NJ, Tegtmeyer K, Zhao J, Worswick S. Dupilumab in Dermatology: Potential for Uses Beyond Atopic Dermatitis. *J Drugs Dermatol*. 2019;18:6. [PMID: 31603635].
5. Rico, Benning, Weingart, Streilein, Hall. Characterization of skin cytokines in bullous pemphigoid and pemphigus vulgaris. *Br J Dermatol*. 1999;140:1079-1086. [PMID: 10354074].
6. Tavakolpour S, Tavakolpour V. Interleukin four inhibition as a potential therapeutic in pemphigus. *Cytokine*. 2016;77:189-195. [PMID: 26440137].
7. Hashimoto T, Kursewicz CD, Fayne RA, Nanda S, Shah SM, Nattkemper L, Yokozeki H, Yosipovitch G, *J Am Acad Dermatol*. 2020;83:53-62. [PMID: 31351883].
8. Ou Z, Chen C, Chen A, Yang Y, Zhou W. Adverse events of Dupilumab in adults with moderate-to-severe atopic dermatitis: A meta-analysis. *Int Immunopharmacol*. 2018;54:303-310. [PMID: 29182975].
9. Kaye A, Gordon SC, Deverapalli SC, Her MJ, Rosmarin D.

Dupilumab for the Treatment of Recalcitrant Bullous Pemphigoid. *JAMA Dermatol*. 2018;154:1225-1226. [PMID: 30140849].

10. Seidman JS, Eichenfield DZ, Orme CM. Dupilumab for bullous pemphigoid with intractable pruritus. *Dermatol Online J*. 2019;25(11). [PMID: 32045153].
11. Abdat R, Waldman RA, de Bedout V, et al. Dupilumab as a novel therapy for bullous pemphigoid: A multicenter case series. *J Am Acad Dermatol*. 2020;83:46-52. [PMID: 32179082].