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Treatment of Bullous Pemphigoid With Dupilumab: A Case Series of 30 Patients

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ABSTRACT

Bullous pemphigoid is often difficult to treat with the limited therapies available. Here, we describe clinical outcomes among 30 adults with bullous pemphigoid patients treated with dupilumab. We performed a multicenter, retrospective case series between March 2020 to August 2022. Patients received a loading dose of dupilumab 600 mg, followed by 300 mg maintenance dose with varying administration frequency tailored to individual patient response. All patients experienced at least some improvement in blister formation and pruritus, with 23 (76.7%) of patients demonstrating either complete clearance of blistering or marked response. Complete clearance of pruritus or marked response was noted in 25 (83.3%) of patients. Eight patients were effectively maintained solely on dupilumab. One (3.3%) patient reported an injection site reaction. Thirty patients represent a small sample, however, to our knowledge, this is the second largest group of BP treated with dupilumab. Furthermore, we provide an understandable framework for clinicians outside of academics to follow and assess treatment responses in their BP patients treated with dupilumab. Dupilumab should be considered as a therapeutic option in patients with bullous pemphigoid given its ability to induce sustained blistering and pruritus response in both typical and refractory cases while maintaining a favorable safety profile.

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INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease, propagated by autoantibodies against BP antigen 230 (BPAG1) and BP antigen 180 (BPAG2).[1] Classically, it presents with intensely pruritic eczematous or urticarial plaques and tense bullae in elderly patients.[1] Less commonly, non-bullous variants occur with eczematous or urticarial plaques alone.[1] Diagnosis relies upon histopathology, direct and indirect immunofluorescence microscopy (DIF/IIF), as well as anti-BP180/BP230 enzyme-linked immunosorbent assay (ELISAs).[1]

Mild or localized disease may be controlled with topical corticosteroids. However, more severe disease is often difficult to treat. Systemic immunosuppression with oral corticosteroids remains the first-line treatment for widespread cases, often leading to detrimental side effects, although effective. Second and third-line agents for recalcitrant disease include a plethora of immunosuppressants such as mycophenolate mofetil, methotrexate, azathioprine, cyclophosphamide, and tetracyclines. Recalcitrant cases are often treated with IVIG and rituximab.

With the further elucidation of humoral immune pathways and the advent of biologics, targeted therapy with rituximab, omalizumab, bertilimumab, and ixekizumab has been used in BP with success.[2] More recently, with the established importance of interleukin (IL)-4 and IL-13 cytokines in autoimmune blistering diseases, the IL-4Rα inhibitor, dupilumab, has risen as a plausible therapeutic option.[3] Several case reports and series have since demonstrated the efficacy of dupilumab in the treatment of BP and other blistering diseases.[4–8,15] Herein, we present the use of dupilumab in 30 patients with BP.

MATERIALS AND METHODS

Study Design

This is a multicenter retrospective case series. De-identified patient data were pooled from various board-certified dermatologists across five institutions: Center for Clinical Studies (Webster, TX), University of Texas Southwestern, University of Washington, Three Rivers Dermatology, and Dermatology Associates of Tallahassee. No washout or change in current blistering therapy was required prior to dupilumab initiation. All patients were loaded with 600 mg at week 0, followed by 300 mg thereafter. All patients started receiving dupilumab in 2-week intervals. The interval was subsequently increased or decreased depending on patient tolerability and symptom recurrence.

Patients

All patients provided consent for the use of their data. Patients were included if they had a clinical examination consistent with BP, DIF, or IIF consistent with BP, and were treated for BP with dupilumab between March 2020 through August 2022. Patient demographics, BP course, and concomitant therapies are available in Table 1.

Outcomes

Response to treatment was determined by improvement in blistering and pruritus and categorized on a 5-point Likert scale in conjunction with endpoints defined by Murrell et al[1]:

1. No response (treatment failure)
2. <25% (minimal response)
3. >25%, <75% (moderate response)
4. >75%, <100% (marked response)
5. 100% (complete remission)

RESULTS

Patients

Of the 30 patients included, there was a 1:1 male-to-female ratio, with a mean age of 75.3 years (range, 60 to 93 years). Idiopathic BP accounted for 26 of 30 cases. Drug-induced BP accounted for the remaining 4 cases. The mean time from diagnosis to initiation of dupilumab was 22.53 months (range, 1 to 120 months). Treatment duration through August 10, 2022, ranged from 2 to 100 weeks. Improvement in blistering and pruritus occurred in all patients. Complete remission of blistering lesions occurred in 15 of 30 cases (50%). Marked response in blistering was noted in 8 other patients (26.7%), whereas moderate and minimal response improvement occurred in 4 (13.3%) and 3 (10%) patients, respectively. Complete remission of pruritus occurred in 16 (53.3%) patients, with 9 others (30%) experiencing marked response, 2 (6.67%) experiencing moderate response, and 3 (10%) experiencing minimal response. Of the 30 BP patients, 9 (30%) were weaned off concomitant treatments and maintained solely on dupilumab. Most patients (22/73.3%) received treatment biweekly. In patients who had a dramatic or complete response, the dosing interval was increased as tolerated. Three patients achieved sustained interval increases (Table 2). Improvement often occurred within 2 to 4 weeks of treatment initiation. Patients with a moderate response noted fewer vesiculobullous lesions and faster healing (partial remission on minimal therapy). Effects were durable with some experiencing disease control for >100 weeks. Only one AE (injection site reaction) was reported, aligning with dupilumab's historical safety profile. One patient died from natural causes. Of the 30 patients, one discontinued treatment due to inadequate response to dupilumab, and two were lost to follow-up; however, the remaining 27 patients desired to continue treatment with dupilumab.

DISCUSSION

In this case series of BP patients treated with dupilumab, all patients experienced at least some improvement in blister formation and pruritus, with 25 (83.3%) of patients demonstrating either complete clearance of blisters or marked response and pruritus resolution in 16 (53.3%) patients. Improvement occurred within 2-4 weeks of treatment initiation in most. Patients with moderate response noted fewer vesiculobullous individual lesions healed faster. Effects were durable with some patients experiencing disease control for greater than >100 weeks. Only one AE (injection site reaction) was reported, aligning with the safety profile seen with the use of dupilumab in other conditions.[9] One patient died secondary to natural causes. Of the 30 patients, one discontinued treatment due to inadequate response to dupilumab, and two were lost to follow-up; however, the remaining 27 patients desired to continue treatment with dupilumab, with some noting it provided just as good or better control than other drugs trialed previously.

Our series reveals flexible individualized treatment with respect to concomitant medications and dosing intervals. In patients not responding to a variety of first and second-line treatments, the addition of dupilumab to concomitant regimens appeared effective and safe. Most patients improved enough to allow tapering of other concomitant medications, and 8 were able to completely discontinue all other systemic medications and be maintained solely on dupilumab. Tapering occurred on a case-

TABLE 1.

Patient Characteristics					
Case	Age/ Sex	Race/ Ethnicity	Comorbidities	Diagnosis	Prior Medications
1	75M	AsA	DM, HTN, HLD, atopic dermatitis	BP	Mupirocin, doxycycline, MMF, triamcinolone orabase
2	74F	W	HLD, GERD, HTN, SCC, Alopecia areata	BP	Rituximab. Azathioprine, Desonide, TAC, prednisone
3	93M	AfA	CKD, HTN, DM, HLD	BP	Doxycycline, TAC Hydroxyzine
4	62M	AfA	Hep C, HTN, Depression/Anxiety, Artthritis, GERD	BP	clobetasol, niacinamide, desoximetasone, Dapsone, MMF, doxycycline, methylprednisolone, prednisone, hydroxyzine
4	62M	AfA	Hep C, HTN, Depression/Anxiety, Artthritis, GERD	BP	clobetasol, niacinamide, desoximetasone, Dapsone, MMF, doxycycline, methylprednisolone, prednisone, hydroxyzine
5	62M	AfA	HTN, Gout, H/o alcohol induced pancreatitis, ischemic stroke, DVT/PE, HSV, GI bleed	BP	IVIG, Rituximab, doxycycline, nicotinamide, methylpredisolone
6	63M	W	HLD, Atopic dermatitis, Parkinson's, traumatic and solar purpura	BP	Prednisone, nicotinamide, cellcept, doxycycline
7	77F	W	Asthma, eosionphilia, GERD, Hypothyroidism, BCC, HLD	BP	Doxycycline, azathioprine, MTX, Rituximab
8	79F	W	steriod induced-hyperglycemia, HTN, HLD, H/o lung adenocarcinoma, H/o AFB infection	BP	Prednisone, Rituximab
9	85F	W	Asthma, CAD, HTN, Glaucoma, HLD, Herpes Zoster	dBP Cipro-floxacin	TAC
10	79M	W	Keratoacanthoma, DM, HTN	BP	Azathioprine, clobetasol, Diprosone, prednisone
11	62F	W	DM, GERD	BP	Prednisone
12	74M	W	DM, GERD, HTN, HLD, CAD, OSA	BP	Prednisone, clobetasol
13	63M	W	CHF, HIV, CRF, OSA, "brain shunt"	BP	Prednisone, levofloxin, doxycycline
14	77M	W	HSV, Anxiety, HTN, HLD	BP	MMF, prednisone
15	77F	W	HTN, Migraine, OA, Ulcers	BP	clobetasol
16	62F	W	HTN	BP	Prednisone, clobetasol
17	81F	W	Diabetes, HTN	BP	Prednisone, clobetasol
18	60F	W	DM	dBP	Prednisone, cyclosporine, Azathioprine,
19	93F	W	HTN, Anxiety	Metfor-min	Fluticasone, prednisone
20	90F	W	H/o Breast cancer, CAD, HTN, Hypothyroidism	BP	TAC (nonadherent)
21	93M	W	HTN, HLD	BP	Prednisone, TAC
22	84F	W	Afib, DM, HTN, HLD, Hypothyroidism	dBP Pio-glitazone OR Lina-gliptin	TAC
23	74M	W	CAD, HTN, DM	BP	Prednisone, Doxycycline,
24	78M	W	CAD, HTN, HLD	BP	Fluocinonide
25	78M	H/W	DM, HTN, HLD, Depression	BP	Topical and systemic steroids, TAC, Doxycycline, Methotrexate, Clobetasol foam, Hydroxyzine
26	77M	AfA	Anemia, DM, HTN, OSA, HLD	BP	Prednisone
27	65F	AfA	COPD, OSA, Hypothyroidism, H/o Hep C, CKD, HTN	BP	Prednisone, TMP/SMX, Minocycline, clobetasol, hydroxyzine
28	82F	AsA	Metastatic melanoma, HLD, Osteopenia, Asthma	dBP Ipi-limumab/ nivolum-ab	TAC, clobetasol, hydroxyzine, prednisone, gabapentin
29	66F	H/W	HTN	BP	prednisone, topical corticosteiods, topical muporicin
30	73M	W	DM, HTN, HLD	BP	prednisone, topical steriods

Abbreviations: Race/Ethnicity: AsA – Asian, W – White, AfA – African American, H/W – Hispanic/White
Comorbidities: DM – diabetes mellitus, HTN – hypertension, HLD – hyperlipidemia, GERD – gastroesophogeal reflux disease, SCC – squamous cell carcinoma, CKD – chronic kidney disease, DVT – deep venous thrombosis, PE – pulmonary embolism, HSV – herpes simplex virus, BCC – basal cell carcinoma, AFB – acid fast bacilli, CAD – coronary artery disease, OSA – obstructive sleep apnea, CHF – congestive heart failure, CRF – chronic renal failure, OA – osteoarthiritis, Afib – atrial fibrillation
Diagnosis: dBP – drug-induced BP

Medications: MMF - mycofenolate mofetil, TAC – triamcinolone, MTX – methotrexate, TMP/SMX – Trimethoprim/Sulfamethexazole

TABLE 2.

Response to Dupilumab								
Case	Time from Diagnosis to Dupilumab Initiation (Months)	Concomitant BP Medications	Treatment Response - Bullae	Treatment Response - Pruritus	Disease Flares	Treatment Duration (Weeks)	Treatment Frequency	Adverse Events
1	48	MMF, Doxycycline, triamcinolone orabase	Complete response	Complete response	N	24	q2wks	None
2	120	Prednisone	Marked response	Complete response	Y	22	q6wks	None
3	60	TAC 0.1% cream, hydoxyzine	Complete response	Complete response	N	20	q8wks	None
4	60	Methylpred taper, TAC 0.1% ointment, Hydroxyzine	Minimal response	Minimal response	Y	48	q2wks	None
5	48	TAC 0.1% ointment, hydroxyzine, Fexofenadine, Gabapentin	Complete response	Marked response	N	56	q2wks	None
6	72	Cellcept, Nicotinamide, Clobetasol, Doxycycline	Moderate response	Marked response	Y	12	q2wks	None
7	40	TAC 0.1% ointment	Complete response	Complete response	N	48	q2wks	None
8	84	TAC 0.1% ointment	Complete response	Minimal response	N	72	q2wks	None
9	1	TAC ointment	Moderate response	Marked response	Y	13	q2wks	None
10	23	Clobetasol cream	Minimal response	Minimal response	Y	14	q2wks	None
11	1	None	Complete response	Complete response	N	4	qweek	None
12	3	TAC	Complete response	Complete response	N	5	q2wks	None
13	1	Prednisone	Complete response	Complete response	N	14	q2wks	None
14	24	None	Complete response	Complete response	N	14	q2wks	None
15	3	Clobetasol	Complete response	Complete response	N	29	q2wks	None
16	2	None	Marked response	Marked response	Y	12	q3wks (nonadherence)	None
17	1	TAC	Moderate response	Marked response	N	12	q2wks	None
18	1	None	Marked response	Complete response	Y	72	q2wks	None
19	1	None	Marked response	Complete response	Y	76	q2wks	None
20	2	None	Complete response	Marked response	N	72	q2wks	None
21	4	TAC	Moderate response	Marked response	N	44	q2wks	None
22	1	Fluocinonide	Complete response	Moderate response	N	6	q2wks	None
23	1	None	Marked response	Complete response	Y	84	q2wks	None
24	1	Halobetasol	Marked response	Marked response	Y	100	q2wks	None
25	36	Azathioprine, Hydroxyzine, TAC, clobetasol	Minimal response	Complete response	Y	2	q2wks	None
26	3	Prednisone	Marked response	Complete response	Y	12	q2wks	None
27	16	Clobetasol, TAC, minocycline	Marked response	Moderate response	Y	45	q2wks	Injection Site Reaction
28	2	prednisone taper	Complete response	Complete response	N	4	q2wks	None
29	10	None	Complete response	Marked response	N	4	q2wks	None
30	7	MTX (tapered from 20 mg to 7.5 mg) weekly	Complete response	Complete response	N	49	q2wks	None

by-case basis, usually following a slow reduction in concomitant medications after the patients were stable for >1 month on dupilumab. Tapering concomitant medications is beneficial as many traditional therapies used for BP carry toxic side effects and require more frequent monitoring when compared to biologics. Moreover, depending on patient responses, some maintenance dosing intervals were increased up to every 8 weeks, thus mitigating the risks and costs that occur with more frequent administration of dupilumab.

Some of the observed benefits seen with dupilumab may be explained by the Th2 dominant response in BP. IL-4 and IL-13 are crucial to propagating this Th2 dominance through their actions on IL4Rα. Both cytokines are produced by Th2 cells, granulocytes, and monocytes/macrophages, and have the potential to promote Th2 and B cell differentiation.[3] Moreover, both amplify IgE and IgG4 production. IL-4 can suppress Th1 cells, resulting in a positive feedback loop which magnifies the Th2 imbalance.[10] IL-4 also contributes to mast cell and eosinophil activation and degranulation.[10]

BP patients harbor a Th2 dominant milieu with overproduction of corresponding cytokines, including IL-4, IL-5, IL-13, eotaxin, chemokine-ligand (CCL)13, CCL17, CCL18, CCL22, and CCL26.[3,4] Autoreactive Th2 cells stimulate proliferation of B cells and causal IgG4 autoantibody production.[11] Th2 cells also contribute to the recruitment and activation of eosinophils.[3] Eosinophils may then promote maintenance of Th2 dominancy via secretion of IL-4, IL-5, and IL-13.[3] These conclusions are supported by studies revealing higher levels of IL-4 and IL-13 in the sera and blister fluid of BP patients.[12] Furthermore, BP patients demonstrate peripheral eosinophilia and elevated IgE in sera.[4,13,14] Concentrations of IL-4, IL-13, eosinophilia, and IgE correlate with disease severity, improving with successful treatment.[4] Dupilumab directly inhibits IL-4 and IL-13, lessening the effects of Th2 imbalance.[4] This modulation also contributes to the downregulation of IgE secretion and eosinophil activity by decreasing B cell proliferation, altering autoantibody production, and decreasing CCL expression.[4]

Dupilumab is also suspected to reduce peripheral itch sensation through inhibition of IL-4 and IL-13 and indirect suppression of IL-31.[4] This likely also contributes to the improvement of pruritus in treated patients. IL-4 and IL-13 play a crucial role in autoantibody formation pathways, isotype switching, Th2 dominance, and eosinophil recruitment in patients with BP. Therefore, through the disruption of these processes, dupilumab has potential as a treatment modality. In our series, dupilumab was useful as a treatment agent for BP via reduction of vesiculobullous lesions, reduction of pruritus, and reduction of concomitant therapies.

Our series reveals flexible individualized treatment with respect to concomitant medications and dosing intervals. Most patients improved enough to allow tapering of other concomitant medications or transition to dupilumab monotherapy. This is beneficial as many traditional therapies used for BP carry toxic side effects and require more frequent monitoring.[2] Moreover, depending on patient responses, some maintenance dosing intervals were increased up to every 8 weeks, thus mitigating the risks and costs incurred with more frequent administration.

DISCLOSURES

Jeffrey Sassmannshausen, MD is a speaker/advisor for Sanofi, Regeneron, AbbVie, Dermavant, and Eli Lilly. The other authors have no conflicts of interest to declare.

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