Dupilumab as a novel therapy for bullous pemphigoid: A multicenter case series

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Background: Bullous pemphigoid (BP) is an autoimmune blistering disorder occurring mostly in the elderly that lacks adequate treatments.

Objective: To describe our experience using dupilumab in a series of patients with BP.

Methods: This is a case series of patients from 5 academic centers receiving dupilumab for BP. Patients were eligible if they had a clinical diagnosis of BP confirmed by lesional skin biopsy evaluated by one of more of the following: hematoxylin and eosin staining, direct immunofluorescence, or enzyme-linked immunosorbent assay for BP180 or BP230, or both.

Results: We identified 13 patients. Patients were an average age of 76.8 years, and the average duration of BP before dupilumab initiation was 28.8 months (range, 1-60 months). Disease clearance or satisfactory response was achieved in 92.3% (12 of 13) of the patients. Satisfactory response was defined as clinician documentation of disease improvement and patient desire to stay on the medication without documentation of disease clearance. Total clearance of the BP was achieved in 53.8% (7of 13) of patients No adverse events were reported.

Limitations: Include small sample size, lack of a control group, lack of a standardized assessment tool, and lack of standardized safety monitoring.

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Drs Abdat and Waldman contributed equally to this article.

Funding sources: None.

Conflicts of interest: Dr Rosmarin has received honoraria as a consultant for AbbVie, Celgene, Dermavant, Dermira, Janssen, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Sun Pharmaceuticals; research support from AbbVie, Bristol-Myers Squibb, Celgene, Dermira, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals; and has served as a paid speaker for AbbVie, Celgene, Janssen, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals, and Sanofi. Dr Nichols has been a consultant for Almirall and Boehringer Ingelheim; and an investigator for Trevi, AbbVie, Boehringer Ingelheim, and Novartis; and starting up a study with Regeneron Pharmaceuticals. Dr King is on the speakers bureau for Pfizer Inc, Regeneron Pharmaceuticals, and Sanofi Genzyme; is an investigator for Concert Pharmaceuticals Inc, Eli Lilly and Company, and Pfizer Inc; and is a consultant to and/or has served on advisory boards for Aclaris Therapeutics, Arena Pharmaceuticals, Concert Pharmaceuticals Inc, Dermavant Sciences, Eli Lilly and Company, and Pfizer Inc. Dr Czernik served as speaker for Genentech. Drs Abdat, Waldman, de Bedout, Mcleod, Gordon, Ahmed, and Rothe have no conflicts of interest to declare.

IRB approval status: The Tufts University Health Sciences Investigational Review Board approved this case series.

Accepted for publication January 15, 2020.

Reprints not available from the authors.

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Published online March 13, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.01.089

Conclusion: Dupilumab may be an additional treatment for BP, leading to disease clearance or satisfactory response in 92.3% of patients, including in those in whom previous conventional therapy had failed. (J Am Acad Dermatol 2020;83:46-52.)

Key words: autoimmune blistering diseases; biologics; bullous disorders; bullous pemphigoid; dupilumab; medications; treatment.

Bullous pemphigoid (BP) is an autoimmune blistering disorder characterized by subepidermal disruption of the structural proteins BP180 and BP230, leading to the formation of tense bullae.[1-4] Type 2 proinflammatory cytokines, including interleukin (IL) 4 and IL-13, may play a role in the pathogenesis of BP through a variety of mechanisms. We hypothesized that dupilumab, an IL-4 receptor-α antagonist, might show efficacy in BP. We report 13 patients with refractory BP who were treated with dupilumab. Response to treatment, time to treatment response, duration of response, and adverse effects are presented.

CAPSULE SUMMARY

- In this multicenter case series of 13 patients, 92.3% with bullous pemphigoid treated with dupilumab achieved disease clearance or a satisfactory response, with 53.8% of patients clearing on dupilumab.
- Dupilumab may represent a new addition to the armamentarium for treatment of bullous pemphigoid.

METHODS

Patients

Patients from Tufts Medical Center, the University of Connecticut Health Center, University of Miami Health System, Mount Sinai Health System, and Yale School of Medicine were included in this case series. The Tufts University Health Sciences Investigational Review Board approved this case series. This was not a prospective study. The corresponding author (D.R.) notified several academic departments of his intention to compile a case series of patients with BP who had received treatment with dupilumab. Other clinicians with patients with BP being treated with dupilumab elected to share deidentified case information with the corresponding author as a part of this case series. Patients were eligible for inclusion if they had:

1. presence of tense bullae on examination and a clinical picture consistent with BP and
2. had a diagnosis confirmed by one or more of the following
   - lesional skin biopsy evaluated by hematoxylin-eosin staining demonstrating a subepidermal blister with eosinophils
   - direct immunofluorescence on normal appearing perilesional skin demonstrating linear deposition of IgG with or without C3 along the basement membrane zone
   - enzyme-linked immunosorbent assay for BP180, BP230, or both

Patients with epidermolysis bullosa acquisita were excluded clinically. Patients without follow-up after initiation of dupilumab were also excluded. Patient medical records were reviewed to assess for treatment response and for adverse events.

Therapy

Patients were treated with dupilumab administered subcutaneously (SC). All patients initially received the dosing regimen approved for atopic dermatitis: 600 mg SC initially, followed by 300 mg SC every other week. The frequency of injections for some partial responders was increased, most commonly to 300 mg SC weekly. No specific washout period was required for patients to switch from immunosuppressive medication to dupilumab. Some patients received other BP-directed therapies concomitantly with dupilumab.

Skin improvement was assessed by the presence of tense blisters and by pruritus assessments. Disease clearance was defined as healing of all previously identified lesions with no new blister formation. Satisfactory response was defined as clinician documentation of disease improvement and patient desire to stay on the medication without documentation of disease clearance. No standardized measurement tool was used for skin evaluation. Coverage for dupilumab was obtained through the patients' insurance and samples.

RESULTS

Patient characteristics

A total of 13 patients with BP were treated with dupilumab. Patient demographics are summarized in Table I.[5] The average duration of BP before dupilumab initiation was 28.8 months (range,

Abbreviations used:

BP: bullous pemphigoid
CCL: chemokine (C-C motif) ligand
IL: interleukin
SC: subcutaneous

1-60 months). One patient was started on dupilumab because systemic therapy was indicated based on the patient's disease severity; however, the patient's other medical comorbidities made conventional systemic therapies undesirable. All other patients were considered to have refractory BP because previous conventional therapy had failed (Table I). The average number of therapies before treatment with dupilumab was 2.5.

Response to dupilumab therapy

Each patient was being managed by a board-certified dermatologist. Patient medical records were reviewed by the clinicians who managed the patients. Disease clearance or satisfactory response to dupilumab was achieved in 92.3% (12 of 13) of patients. Satisfactory response was defined as documented clinical improvement and patient desire to continue dupilumab. Disease clearance, defined as an absence of both bullae and pruritus, was achieved in 53.8% (7 of 13). To be considered to have achieved disease clearance, patients must have maintained disease clearance at their most recent clinic visit. Of those achieving disease clearance, 42.9% (3 of 7) received dupilumab more frequently than every other week. The dosing frequency of 1 patient was increased to every 12 days after being on dupilumab for 3 months because he reported breakthrough pruritus 12 days after each injection. The other 2 patients received dupilumab weekly. The rest of the patients were receiving dupilumab 300 mg every other week.

Dupilumab was efficacious in reducing both bullae formation and pruritus. The bullae in 76.9% (10 of 13) of patients resolved with residual pruritus (Figs 1 and 2). Objective improvement of pruritus was reported by 11 of 13 patients (84.6%), with 7 of 11 patients experiencing complete resolution of their pruritus. One patient reported improvement in his pruritus but still had persistent bulla. Only 1 patient had no improvement in itch or bulla formation. This nonresponder and all satisfactory responders in whom disease clearance was not achieved were receiving dupilumab 300 mg every other week.

Three patients in our case series achieved disease clearance while receiving dupilumab in conjunction with conventional therapy. One of these patients received methotrexate in conjunction with dupilumab 300 mg every other week. She had been receiving a stable dose of methotrexate with inadequate disease control for more than 1 year before dupilumab initiation. She achieved disease clearance 2 months after initiating dupilumab and is now tapering her methotrexate without disease rebound.

Another patient was initially treated with dupilumab together with prednisone 1 mg/kg/d. This patient had rapid disease clearance and was successfully tapered off prednisone over 12 weeks. The patient subsequently maintained disease clearance on dupilumab monotherapy until she accidentally discontinued dupilumab, which resulted in disease flare. She subsequently restarted dupilumab monotherapy and cleared within 1 month.

The third patient achieved clearance with intravenous immunoglobulins for 1 month before flaring on her face and extremities. This patient cleared within 8 weeks of starting dupilumab 300 mg weekly and was successfully tapered off methotrexate. She recently discontinued dupilumab during hospitalization for repair of gastric ulcer and new blisters and worsening pruritus developed 1 month later.

Although the disease clearance rate of patients receiving dupilumab plus concomitant immunosuppressive (7 of 12) was higher than the disease clearance rate for patients receiving dupilumab monotherapy (5 of 12), we believe this finding is spurious, because the patients receiving concomitant immunosuppressive therapy were being tapered off their immunosuppressive agent without any worsening of their disease.

The duration of dupilumab therapy averaged 5 months. The average time to response cannot be determined with precision because each physician used different follow-up intervals; however, all responders responded in within a median of 2 months (range, 1-5 months) of treatment initiation. Furthermore, 5 patients reported improvement in pruritus and bullae within 1 month of treatment initiation, with 2 of 5 patients responding within 2 weeks of treatment initiation. There were no records for time of first improvement for 4 patients. All physicians independently recorded that patients reported improvement in pruritus after receiving their loading doses of dupilumab.

Therapy was unintentionally disrupted in 2 patients who initially cleared within 1 to 3 months of dupilumab initiation, which triggered a disease flare. These patients subsequently restarted dupilumab, and both fully recaptured their previous response.

No specific monitoring for adverse events was performed because this was not a prospective study; however, all patient records were reviewed for

Table I. Patient characteristics and dupilumab therapy

Patient	Age, y	Sex	Diagnostic confirmation	Duration from diagnosis to dupilumab initiation	Systemic medications before dupilumab	Concomitant medications with dupilumab	Response to dupilumab
1*	83	M	H&E and DIF	2 years	Prednisone, was not eligible for mycophenolate due to positive hepatitis B core antibody and QuantiFERON-TB Gold† positive	None	Disease clearance‡
2	78	F	H&E and serology	5 years	Prednisone, mycophenolate, doxycycline and niacinamide	None	Disease clearance‡
3	70	F	H&E, DIF and serology	3 months	Prednisolone, MTX, IVIG	MTX weekly (tapered from 20 to 7.5 mg)	Disease clearance‡
4	77	M	H&E and DIF	1 year	Doxycycline	None	Disease clearance‡
5	81	M	H&E, DIF, and serology	1 month	None	None	Improvement of pruritus but no clearance of bulla
6	86	M	H&E and serology	5 years	Prednisone, MTX	None	Improvement of pruritus and clearance of bulla after 1 month of dupilumab treatment
7	83	F	H&E, DIF, and serology	1 month	Prednisone, doxycycline, and niacinamide	Prednisone 60 mg daily at the time of dupilumab initiation, then tapered by 5 mg weekly; off prednisone in 3-month period	Disease clearance‡
8	71	F	Clinical diagnosis	Unclear, diagnosis was made before the patient presentation to UConn Health Center. Patient was referred with diagnosis of BP and referral paperwork is not present in current EMR	MTX	MTX tapered from 12.5 mg to 10 mg weekly	Disease clearance‡
9	53	F	H&E and DIF	4 years	Rituximab, IVIG, doxycycline, nicotinamide, and azathioprine	None	No improvement in pruritus or bulla; dupilumab was discontinued in 8 weeks

Continued

Table I. Cont'd

Patient	Age, y	Sex	Diagnostic confirmation	Duration from diagnosis to dupilumab initiation	Systemic medications before dupilumab	Concomitant medications with dupilumab	Response to dupilumab
10	86	M	H&E and serology	3 years	Prednisone, mycophenolate, rituximab, and IVIG	Intralesional (20 mg/mL) and topical steroids	Improvement in pruritus and clearance in bulla after 3 months of dupilumab
11	91	M	H&E and DIF	3 years	Prednisone, MTX	MTX 10 mg weekly	No improvement in pruritus and clearance of bulla after 4 months of dupilumab treatment
12	76	M	H&E, DIF and serology	3 months	Prednisone	Taper course of prednisone	Disease clearance[‡]; patient flared after discontinuing dupilumab
13	64	M	DIF and serology	5 months	Prednisone	Taper course of prednisone, now off	Improvement of pruritus and bulla

BP, Bullous pemphigoid; *DIF*, direct immunofluorescence; *EMR*, electronic medical record; *F*, female; *H&E*, hematoxylin and eosin; *IVIG*, intravenous immunoglobulin; *M*, male; *MTX*, methotrexate; *UConn*, University of Connecticut.
*Patient case was previously published.[5]
[†]QIAGEN, Germantown, Maryland.
[‡]Defined as resolution of pruritus and clearance of bulla.

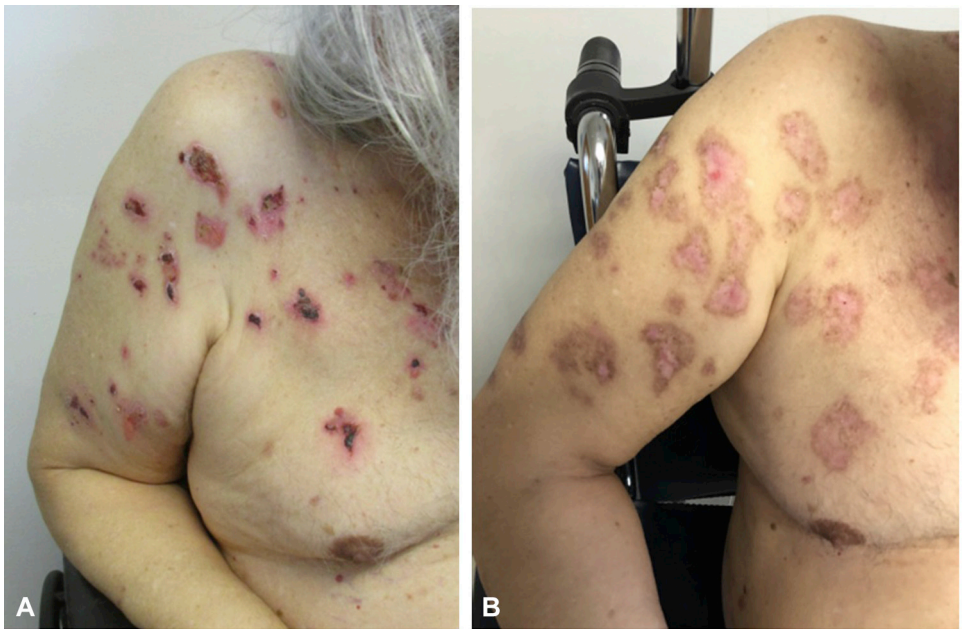

Fig 1. (**A**) Bullous pemphigoid before dupilumab in patient 4. A hemorrhagic crusting and tense bullae on the right chest and upper arm. (**B**) Bullous pemphigoid resolved after dupilumab in patient 4. Hyperpigmented patches in the absence of any bullae or crusting 2 months after starting dupilumab.

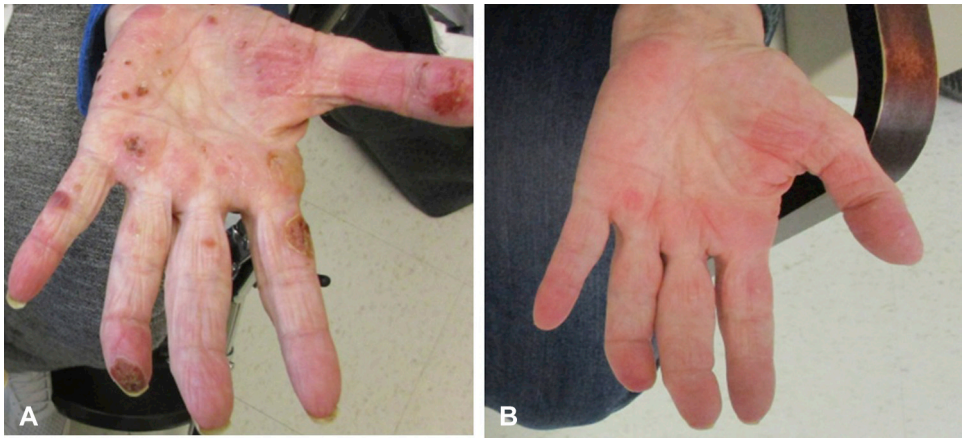

Fig 2. (**A**) Tense bullae, hemorrhagic crusting, and erythematous patches on the bilateral palms in patient 3. (**B**) Slight erythema of the palmar hands in patient 3 in the absence of bulla 1 month after starting dupilumab.

adverse events, with specific assessment for allergic reactions, infections, dupilumab ocular surface disease, and dupilumab facial redness. No adverse events were reported or documented in patient medical records. No patients discontinued due to adverse events.

DISCUSSION

Our case series describes 13 patients with BP who received dupilumab Of these, 53.8% (7 of 13) of our patients achieved disease clearance, and an additional 34% achieved satisfactory disease control in pruritus or bullae clearance defined as a patient-reported desire to continue on the medication. Only 1 patient did not improve on dupilumab.

Dupilumab was well tolerated in our study population, with no reported dupilumab-attributed adverse events. Additionally, no adverse events were associated with increased frequency of dupilumab administration. Analogous to eosinophilic esophagitis in which weekly dosing may be necessary,[6] higher doses of dupilumab may be necessary for some patients with BP because the presumed mechanism of action in BP involves downstream eosinophil inhibition.

We attribute the observed efficacy of IL-4 and IL-13 inhibition in this study to the pleiotropic effects of these cytokines. Most patients with BP have increased numbers of cells producing IL-4 and IL-13 in sera and blister fluid, both of which have been shown to decrease with successful disease treatment.[7] Patients with BP also exhibit elevated circulating levels of immunoglobulin E and peripheral eosinophilia, which correlate with disease activity.[8,9] Dupilumab addresses these disease biomarkers by directly inhibiting IL-4 and IL-13 signaling. It also indirectly downregulates immunoglobulin E secretion and eosinophil activity through the following mechanisms: (1) inhibiting preactivated B-cell proliferation; (2) directing human B lymphocytes to switch to IgG4 and immunoglobulin E synthesis; and, (3) downregulating eosinophil chemotaxis and helper T cell type 2–associated chemokine activity (chemokine [C-C motif] ligand [CCL] 17, CCL18, CCL22, and CCL26) without significant modulation of helper T cell type 1–associated genes.[10,11]

Dupilumab may improve pruritus by decreasing peripheral itch sensory neuron signaling through its direct effects on IL-4 and IL-13 and through its effects on eosinophils that result in decreased IL-31 secretion.[12]

Limitations of this study include a small sample size, lack of a control group, lack of a standardized assessment tool, and lack of standardized safety monitoring. In addition, this study's inclusion criteria are not previously validated criteria, and therefore, they may not include all cases of BP and may allow for inclusion of cases of non-BP immunobullous diseases (eg, inflammatory epidermolysis bullosa acquisita). One patient in this series does not have documented laboratory confirmation of her diagnosis.

CONCLUSION

Our multi-institutional study suggests that dupilumab may be an additional treatment for BP, leading to disease clearance or satisfactory response in 92.3% of patients. If future studies confirm efficacy and tolerability, an immunomodulatory (rather than immunosuppressive) therapy such as dupilumab would be a welcome addition to the BP treatment armamentarium.

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