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CASE REPORT

Dupilumab as Immunomodulatory Rescue for Severe Recalcitrant Pemphigus Vulgaris: A Case Report and Literature Review

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Abstract: Standard treatment of pemphigus vulgaris (PV) includes corticosteroid, immunosuppressants, and biologics such as rituximab, a monoclonal antibody targeting $CD20^+$ B cells. However, some patients develop resistance to rituximab, requiring alternative therapeutic approaches. We report a 15-year-old female with severe PV who developed rituximab refractoriness after an initially effective response. Despite treatment with a combination of intravenous immunoglobulin, corticosteroid, and immunosuppressants, the patient failed to achieve disease control. Consequently, dupilumab, an interleukin-4 receptor α antagonist, was initiated on a biweekly regimen. Her lesions showed dramatic improvement, with the pemphigus disease area index (PDAI) reaching 0. Her anti-desmoglein 1 antibody level became negative, and T helper (Th)-2 inflammatory markers, including eosinophil count and immunoglobulin E (IgE) level, was normalized, allowing corticosteroid tapering after the 8th dose (last dose) of dupilumab. She has maintained complete remission for at least 28 weeks with regular follow-ups. We additionally propose possible mechanisms underlying rituximab refractoriness and how dupilumab modulates this treatment response. Our case highlights dupilumab's potential in modulating Th-2-driven autoantibody production for PV patients with high peripheral eosinophils and IgE levels who have severe disease resistant to corticosteroids or rituximab.

Plain Language Summary: This is a report on a case with severe pemphigus vulgaris (PV) unresponsive to rituximab (anti-CD20) and successfully treated with dupilumab (anti-IL4Rα), suggesting a potential role for dupilumab in severe recalcitrant PV.

Keywords: pemphigus vulgaris, bullous disease, autoimmune disease, dupilumab, type 2 immune response, rituximab

Introduction

Pemphigus vulgaris (PV) is a chronic, immunoglobulin (Ig) G-mediated autoimmune blistering disorder characterized by the presence of autoantibodies against desmoglein 1 (Dsg1) and 3 (Dsg3), which are critical components of keratinocyte adhesion in the skin and mucosa. The resulting loss of intraepidermal cell-cell adhesion leads to the formation of flaccid blisters that easily rupture, leaving painful erosions on the skin and mucous membranes.[1,2]

Standard treatment typically involves topical and systemic corticosteroids combined with immunosuppressants (such as azathioprine and mycophenolate mofetil) and biologics, such as rituximab (a monoclonal antibody targeting $CD20^+$ B-cell rituximab), aiming to suppress autoantibody production.[3–5] However, some patients, particularly those with severe presentations, may exhibit only a partial response or resistance to standard treatment. In such cases, high dose intravenous immunoglobulin (IVIG), which modulates Fc receptors (FcRs) on immune cells that can bind with circulating anti-desmoglein antibodies, may be recommended.[3,6] According to advanced developments, novel biologics can theoretically inhibit autoantibody production.[7] Specifically, dupilumab, which can inhibit action of interleukin (IL)-4 and IL-13, the main cytokines of T helper (Th)-2 cells that trigger B-cells to produce the autoantibodies, has been suggested as an emerging treatment for PV.[7–10]

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In this report, we present the case of a 15-year-old female with severe PV who developed resistant to rituximab following an initial effective response. Through the administration of dupilumab, an IL-4 receptor alpha (IL-4Rα) antagonist, we achieved remarkable disease control and improved her quality of life. Additionally, we propose potential mechanisms of rituximab refractoriness in PV. This case highlights the role of dupilumab as a treatment option for severe recalcitrant PV.

Case Presentation

A 15-year-old Thai female was diagnosed with severe PV at the age of 12. The diagnosis was based on classic presentations (crusted erosion and flaccid bullae over face, trunk, extremities, and mucosa), histological findings (suprabasal separation with acantholysis), and laboratory findings (anti-Dsg1 > 200 U/mL and anti-Dsg3 = 39.6 U/mL). She had been treated with rituximab, azathioprine, and prednisolone as shown in the medication timeline (Figure 1a). After the 1st rituximab infusion of 1000 mg administered 2 weeks apart, her pemphigus disease area index (PDAI) improved for 13 months before the 1st relapse. She was then treated with the 2nd infusion of rituximab, which led to an improvement in her PDAI for 12 months, together with the tapering off prednisolone before the 2nd relapse. However, after the 3rd infusion of rituximab, the dosage

a

Disease course

Age (years)	12			13			14					15					
Follow up (month)	Aug.	Sep.	Nov.	Aug.	Nov.	Dec.	Jan.	Feb.	Mar.	Jun.	Oct.	May	Jun.	Jul.	Aug.	Sep.	Oct.
Clinical score																	
PDAI	20		3	0	30	22	6	3	4		0	7	42		28	31	82
ABSIS					17.5							1.5	30.5				
Laboratory results																	
Blood eosinophil					2%		0%	6%	7%	1%	4%	9%	15%	25%	29%	8%	18%
Anti-Dsg1 (U/mL)	>200		71.72		>200			16.37			13.53				79.02		57.67
Anti-Dsg3 (U/mL)	39.6		90.76		>200			172.2			>200				>200		>200
Medications for PV																	
Prednisolone (mg/day)	20	20	15	7.5	30	30	20	15	10	off	off	10	25	30	45	30	15
Azathioprine (mg/day)	25	50	50	50	50	50	50	75	100	100	50	50	off	off	50	75	50
Rituximab (cycle)		1st				2nd								3rd			

1st relapse

2nd relapse

b

~ 2.5 months following the 3rd cycle of rituximab

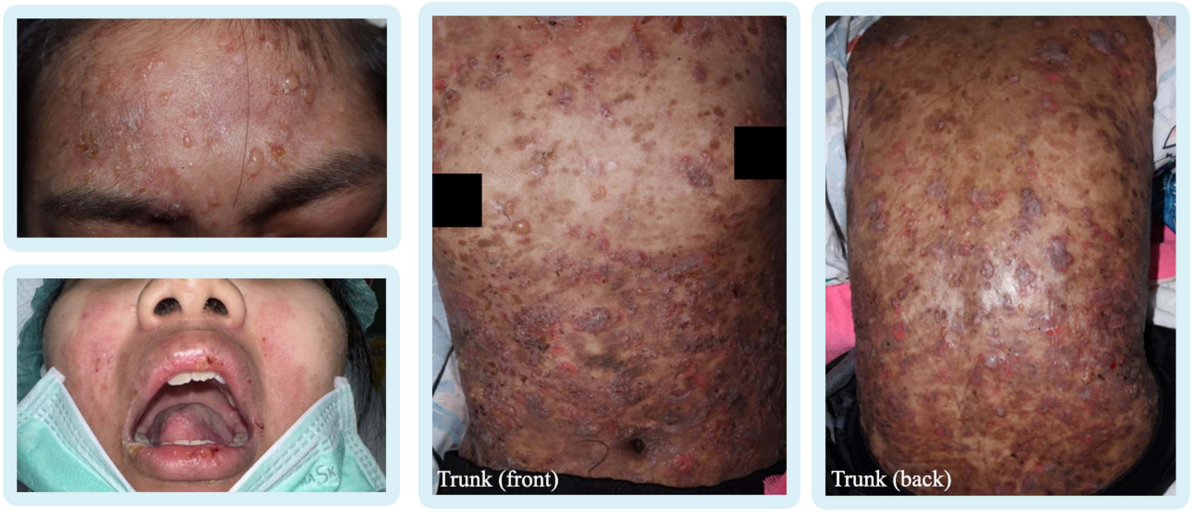

Figure 1 Disease course and clinical pictures. A Thai female was diagnosed with severe PV at the age of 12. (**a**) Her disease course and (**b**) clinical pictures at 2.5 months following the 3rd cycle of rituximab, when her PDAI was 82, are shown. The normal range for anti-Dsg1 and Dsg3 is less than 20 U/mL.
Abbreviations: ABSIS, autoimmune bullous skin disorder intensity score; Dsg, desmoglein; mg, milligram; PDAI, pemphigus disease area index; PV, pemphigus vulgaris; U/mL, units per milliliter.

of prednisolone could not be tapered off, and her PDAI did not improve or achieve control. At 2.5 months after the 3rd rituximab infusion, she presented with generalized flaccid bullae and crusted erosions on erythematous patches involving her face, trunk, and extremities. Additionally, her nasal mucosa, upper gingiva, lips, and genitalia exhibited multiple crusted erosions. The estimated affected body surface area exceeded 90%, her PDAI reached 82, her peripheral blood eosinophil count was 3,355 cell/mm^3 (18%) with an IgE level of 3,171 IU/mL, and her anti-Dsg3 antibody level was greater than 200 U/mL and anti-Dsg1 antibody level was 57.68 U/mL (Figure 1a and b). She was admitted with a diagnosis of severe PV. Due to suspected recalcitrance to rituximab, we decided to administer 2 g/kg per cycle of IVIG along with corticosteroids to control the severe PV. She was discharged with marginal improvement in her skin lesions. IVIG was continued every 4 weeks together with 10−20 mg/day of prednisolone. Despite the administration of 3 cycles of IVIG, new bullous lesions continued to erupt, and the PDAI remained high. Given the recalcitrant nature and following a re-biopsy confirming PV (Figure 2a and b), we decided to initiate treatment with dupilumab. The regimen included a 600 mg subcutaneous loading dose, followed by 300 mg every 2 weeks (Figure 2c). Remarkably, her skin and mucosal lesions progressively improved, with no new eruptions starting 2 weeks after dupilumab. IVIG was discontinued after 6 cycles. Dupilumab treatment has been continuing, achieving a PDAI of 0 after the 8th dose. Her anti-Dsg1 antibody level decreased to 7.52 U/mL (negative); however, anti-Dsg3 antibody level remained detectable at >200 U/mL. Her blood eosinophil count decreased to 468 cells/mm³ (4.4%), and her IgE level decreased to 1,038 IU/mL (↓67.27%). With continued disease control, prednisolone was gradually tapered to 7.5 mg/day (Figure 2c and d). Dupilumab was then discontinued where she maintained complete remission (CR) on minimal therapy for at least 28 weeks with continued regular follow-ups.

Discussion

The standard treatment for severe PV is rituximab, a chimeric monoclonal antibody that targets CD20$^+$ B-cells. It results in B-cell depletion, a decrease in desmoglein antibody production, and subsequently, an effective improvement in blister lesions.[3,11] However, some patients may develop recalcitrance or resistance to the standard treatment. In such cases, considering other biologic drugs that can theoretically target mechanisms in the complex pathogenesis of PV could be effective. Here, we present the successful treatment of a severe case with recalcitrant to rituximab and combined immunosuppressants using dupilumab.

We suggest that several potential mechanisms contribute to recalcitrance to rituximab in our patient, highlighting the need for alternative therapies. First, rituximab primarily depletes CD20$^+$ B-cells. However, CD20$^-$ long-lived plasma cells (LLPCs), which sustain anti-desmoglein antibodies, continue to drive disease activity after CD20$^+$ B-cell depletion.[11,12] Second, a decrease in CD20 expression on B-cells after multiple administration of rituximab treatment may present similarly to B-cell non-Hodgkin lymphoma resistance to rituximab.[13] Third, anti-rituximab antibodies may be presented after rituximab administration.[14] Fourth, our patient may have a persistent autoreactive IL-4 secreting Th-2 cell stimulating B-cell differentiation.[15] The recognition of T-cells to different domains of desmoglein may result in variations in immune response in PV, as evidence has revealed an increased type 2 T-cell response upon T-cell recognition of the Dsg3 ectodomain.[9,16] Finally, the patient may have persistent eosinophil-driven inflammation, as evidenced by hypereosinophilia and an elevated IgE level in our case. Eosinophils release cytotoxic granules, exacerbating keratinocyte damage and blister formation. Their activation is primarily driven by Th-2 cytokines (IL-4 and IL-13) and further amplified by IgE-mediated degranulation, which is promoted by IL-4-induced class switching.[10] Interestingly, since rituximab does not significantly reduce IgE levels,[17] robust inflammation due to IgE aggravation may ensue. Additionally, ARPIL (a proliferation-inducing ligand) and IL-6 released by eosinophil contribute to the survival of LLPCs and auto antibody production.[18] Given these potential mechanisms of rituximab resistance, we considered alternative therapeutic targets to suppress autoantibody production. While IVIG modifies FcRs on immune cells to prevent circulating anti-desmoglein antibodies from binding and neutralizing downstream signals, it does not address ongoing antibody production, which may lead to clinical recalcitrance. Therefore, dupilumab emerged as a viable therapeutic alternative in our case.

Dupilumab, a humanized IgG monoclonal antibody that blocks IL-4Rα, thereby inhibiting the actions of IL-4 and IL-13, may modulate autoantibody production through several mechanisms. First, dupilumab blocks IL-4, which inhibits Th-2 differentiation and reduces the type 2 immune response, leading to a balanced Th-2:Th-1 activity[10] and modulation of

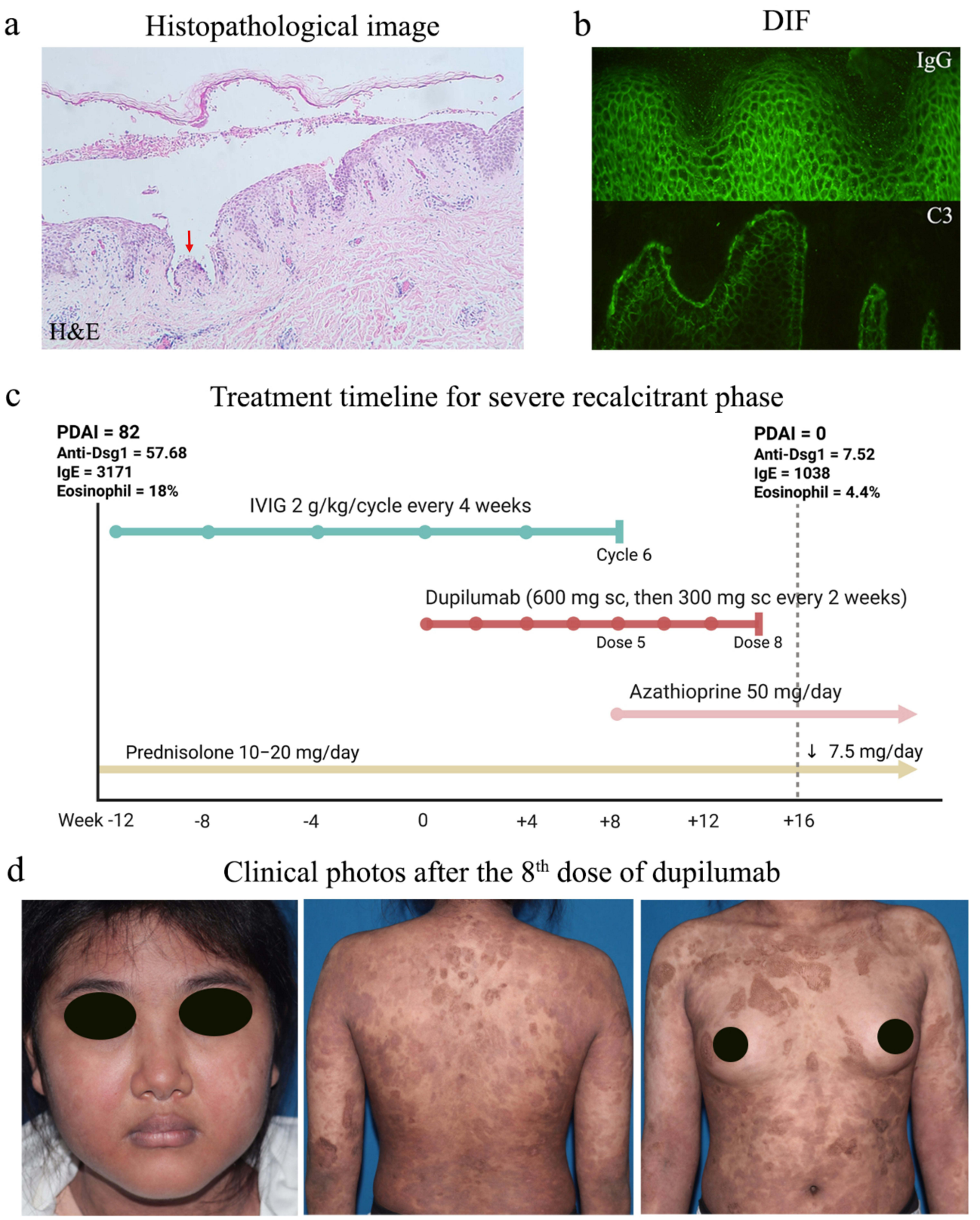

Figure 2 Treatment timeline for severe PV and clinical pictures of improvement. (**a**) Histopathological image revealed suprabasal separation of the epidermis (arrow) with acantholytic cells. (**b**) Direct immunofluorescence (DIF) images revealed intercellular deposition of IgG and C3 at the epidermis. (**c**) The treatment timeline for recalcitrant PV. (**d**) Clinical pictures following the 8th dose of dupilumab are shown.

Abbreviations: C, complement component; Dsg, desmoglein; H&E, hematoxylin and eosin; g, gram; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; kg, kilogram; mg, milligram; PDAI, pemphigus disease area index; PV, pemphigus vulgaris; SC, subcutaneous injection.

Table 1 Dupilumab Treatment Outcomes in Pemphigus Cases

Year/Author	Age (Years Old)/Sex	Race	Presentation	Skin Histopathology	DIF	Pemphigus Type and Concurrent Disease	Refractory Treatment	Treatment	Improvement	PDAI		Immunology Lab	
										Before	After	Before	After
2025, our case	15/Female	Thai	Crusted erosion and flaccid bullae over face, trunk, extremities, and mucosa	Suprabasal separation with acantholysis	DIF: Intercellular deposition of IgG and C3 at the epidermis	Pemphigus vulgaris	Combination of rituximab, prednisolone and azathioprine	Combination therapy Initial phase: Dupilumab 600 mg SC, then 300 mg SC every 2 weeks + 2 g/kg/cycle of IVIG every 4 weeks + prednisolone Maintenance: Dupilumab 300 mg SC every 2 weeks + prednisolone + azathioprine	2nd week: no new lesion 14th week: clear	82	0	- Anti-Dsg3 = 39.6 U/mL - Anti-Dsg1 > 200 U/mL - Serum IgE = 3,171 IU/mL - Peripheral blood eosinophil = 3,344 cell/mm^3	- Anti-Dsg3 = 7.52 U/mL (negative) - Anti-Dsg1 > 200 U/mL - Serum IgE = 1,038 IU/mL - Peripheral blood eosinophil = 468 cell/mm^3
2023, Jiang C et al,[21]	47/Male	Hispanic	Eroded plaques on left hand, plaque with eroded bullae on his dorsal aspect of forearms and left breast Lesions on face and abdomen Oral mucosal lesion	Hematoxylin-eosin stain was done (no description)	DIF was done (no description)	Pemphigus vulgaris	Combination of rituximab, prednisolone, mycophenolate mofetil (dosage is not mentioned)	Combination therapy Initial phase: Dupilumab 300 mg SC every 2 weeks (started at 1 month after single dose of rituximab) (total doses were not mentioned) Maintenance: Dupilumab 300 mg SC every 6 weeks + prednisolone	20th week (completed resolution): hand 40th week (completed resolution): forearms	N/A	0	N/A	N/A
2023, Jiang C et al[21]	80/ Male	Asian American	Painful oral ulcers Ulcerated plaques and flaccid bullae on scalp	Hematoxylin-eosin stain was done (no description)	DIF was done (no description)	Pemphigus vulgaris	Combination of prednisolone and azathioprine	Combination therapy Dupilumab 300 mg SC every 2 weeks + prednisolone + azathioprine	Due to the development of new painful oral ulcers and blisters on the scalp, shoulders, and back at the 4th week, dupilumab was discontinued (short observation)	N/A	N/A	N/A	N/A
2022, More AY et al[22]	41/Female	American	Superficial bullae and crusted erosions on buccal/lingual mucosa, scalp, chest, abdomen, back, legs, and groin for 4 months	Suprabasal acantholysis with separation of superficial epidermis overlying dermal infiltration of lymphocytes, histiocytes, and scattered eosinophils.	DIF: Intercellular deposition of IgG and C3 at the epidermis	Pemphigus vulgaris	Several courses of systemic corticosteroid	Monotherapy: Dupilumab 600 mg SC, then 300 mg every 2 weeks for 2 cycles, then 300 mg weekly	– 2nd week: Scalp and truncal lesion – 6th week: Oral lesion	N/A	N/A	N/A	N/A

(*Continued*)

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Table 1 (Continued).

Year/Author	Age (Years Old)/Sex	Race	Presentation	Skin Histopathology	DIF	Pemphigus Type and Concurrent Disease	Refractory Treatment	Treatment	Improvement	PDAI		Immunology Lab	
										Before	After	Before	After
2022, Chen S et al[23]	35/Male	Chinese	Blister and ulcer on oral mucosa, trunk, genitalia, and extremities for 6 months	Intraepithelial cleavage with detached keratinocytes primarily localized to the suprabasal region	DIF: Spinosum intercellular deposition of IgG and C3	- Pemphigus vulgaris - Pulmonary tuberculosis - Suspected bacterial or tuberculous intracranial infection or sepsis	40 mg methylprednisolone daily	Combination therapy - Dupilumab 600 mg SC (weeks 0 and 2), then 300 mg SC every 2 weeks - 15 g IVIG for 4 days -Methylprednisolone 40 mg daily - Anti-TB drug - Antibiotic	6th week	97	42	Serum IgE = 374 IU/mL Peripheral blood eosinophilia = 1.04×10^9 /L	Serum IgE = 97.9 IU/mL Eosinophil = 0.19×10^9 /L
2023, Jiang C et al[21]	55/Male	Asian American	Multiple scaly and ulcerated plaques and flaccid bullae on neck, chest, and scalp No mucosal lesion	Histopathology was done (no description)	DIF: Intercellular deposition of IgG, negative for IgM and C3	- Pemphigus foliaceus	Multiple courses of systemic corticosteroid	Initial phase: Dupilumab 600 mg SC, then 300 mg SC every 2 weeks Maintenance phase: Dupilumab 300 mg SC every 8 weeks	60th week (completed resolution)	N/A	0	N/A	N/A
2023, Chen J et al[24]	39/Male	Chinese	Blistering and ulceration on face, trunk, and extremities	Intraepithelial cleavage with detached keratinocytes primarily localized just under the stratum corneum.	DIF: Spinosum intercellular deposition of IgG and C3	Pemphigus erythematosus	40 mg of methylprednisolone daily	Combination therapy Initial phase: Dupilumab 600 mg SC weekly + methylprednisolone 40 mg daily for 10 months Maintenance: Dupilumab 300 mg SC monthly + methylprednisolone 4 mg one daily	3rd week	40	0	Serum IgE = 329 IU/mL	Serum IgE = 234 IU/mL
2023, Chen J et al[24]	59/Female	Chinese	Erosions on the face, trunk, and extremities for more than 10 years	Subcorneal split directly below the stratum corneum	DIF: Spinosum intercellular deposition of IgG and C3	Pemphigus erythematosus	12–16 mg methylprednisolone daily (combined with doxycycline, mycophenolate mofetil, and methotrexate)	Combination therapyInitial phase: Dupilumab 600 mg SC, then 300 mg SC weekly + methylprednisolone 16 mg daily for 5 months. Maintenance: Dupilumab 300 mg SC every 2 weeks + methylprednisolone 8 mg	4th week	50	6	N/A	N/A

Abbreviations: C, complement component; DIF, direct immunofluorescence; g, gram; Ig, immunoglobulin; IU/mL, international units per milliliter; IVIG, intravenous immunoglobulin; mg, milligram; N/A, not available; PDAI, pemphigus disease area index; SC, subcutaneous injection; U/mL, units per milliliter.

persistent Th-2-driven B-cell activation.[9,19] Second, dupilumab may reduce the replenishment of pathogenic CD20 plasma cells by preventing IL-4 from stimulating autoreactive B-cells into antibody-secreting plasma cells.[9,19] Third, dupilumab may inhibit eosinophil-stimulated B-cell activation and IgE class switching, given that IL-4 and IL-13 act as eosinophil chemoattractant and IgE switch inducers.[10,19] Additionally, IL-13 contributes to epithelial barrier dysfunction and chronic inflammation. By blocking IL-13, dupilumab helps restore skin integrity and reduce chronic inflammation.[20] In our patient, the PDAI decreased dramatically, reaching 0 after the 8th dose, together with the normalization of peripheral blood eosinophils, the reduction in IgE level, and the negative anti-Dsg1 antibody. These allowed the tapering of the prednisolone, suggesting effective disease control. Although anti-Dsg3 antibody was still detectable, its initial level might have been extremely high, beyond the reportable range. Therefore, we suspect that dupilumab could be an alternative treatment option in severe recalcitrant PV patients especially when they possess high peripheral eosinophils and/or IgE levels which translates to a dominant type 2 immune response and Th-2 driven B-cell activation.

There have been cases of pemphigus that failed to respond to corticosteroid or rituximab but were successfully treated with dupilumab, as shown in Table 1. Dupilumab dosage was initiated at 600 mg subcutaneously, followed by 300 mg every 1–2 weeks in the initial phase, and then 300 mg subcutaneously every 2–8 weeks for the maintenance phase. We noted that hypereosinophilia and an elevated IgE levels may serve as an additional predictor of dupilumab responsiveness in patients with pemphigus. In addition, dupilumab has also demonstrated promise in treating other bullous diseases, particularly bullous pemphigoid and linear IgA bullous dermatosis, which are characterized by subepidermal blistering and severe pruritus.[25,26] While not exclusively Th-2-driven, Th-2 cell activity contributes significantly to their pathogenesis, similar to its role in pemphigus.

In conclusion, we present a case of severe rituximab-refractory PV successfully treated with dupilumab, propose potential mechanisms of rituximab refractoriness. By blocking Th-2-driven auto-antibody production and inflammation, dupilumab offers the novel immunomodulatory strategy for patients with severe PV. This includes patients who are resistant to rituximab and/or corticosteroid, or who exhibit hypereosinophilia or elevated IgE levels, or patients who are complicated by severe infections. When combined with IVIG, corticosteroid, and low dose immunosuppressants such as azathioprine, it serves as a meaningful approach to achieving disease control. Further studies on the immunomodulatory rescue with dupilumab is warranted to fully define its treatment course and long-term safety profile for patients with PV.

Data Sharing Statement

The data supporting this report are available from the corresponding author upon reasonable request.

Consent Statement

The patient's parent provided written informed consent for the publication of this case report and any accompanying images.

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Disclosure

The authors have no conflicts of interest in this work.

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