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Review Article

A Systematic Evaluation of Dupilumab for Bullous Pemphigoid Treatment

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This paper systematically reviews the current articles regarding the use of dupilumab in the treatment of bullous pemphigoid (BP) to evaluate its safety and efficacy. PubMed, Embase, Cochrane Library, and Web of Science databases were searched for publications on dupilumab for BP from inception to 10 March, 2023. A total of 26 studies were included for systematic review. The primary outcome was clinical remission, and the secondary outcomes were recurrence and adverse events. Among 96 patients, 71.8% ($n = 69/96$) received systemic or topical steroids, immunosuppressants, immunomodulators, intravenous immunoglobulins, antihistamines, plasmapheresis, rituximab, and omalizumab, but none of them were successful. After dupilumab treatment, 66.7% ($n = 64/96$) of patients achieved complete remission, 25.0% ($n = 24/96$) had partial remission, 5.2% ($n = 5/96$) showed no remission, and no patients experienced deterioration. In addition, 1.0% ($n = 1/96$) and 2.0% ($n = 2/96$) patients stopped using dupilumab due to adverse reactions and cost, respectively. The average remission time was 4.5 months. 46.2% ($n = 25/96$) of the patients were followed up with a median follow-up of 8 months and only 2 patients relapsed at 8 and 7 months, respectively. Adverse event was 16.9% ($n = 12/71$), of which transient eosinophilia was the most common. This study indicates that the dupilumab is a promising treatment for BP with high clinical benefit associated with low recurrence rate, adverse event rate, and mortality. However, a large-scale randomized controlled trial is needed to further confirm the safety and efficacy of dupilumab in patients with BP treatment.

1. Introduction

Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering diseases clinically characterized by blisters or/and erosions of the skin and mucosa with severe pruritus, mainly affecting individuals aged more than 60 years old worldwide [1]. As aging advances by leaps and bounds, the world incidence and prevalence of BP is increasing. The cumulative incidence of BP is 8.2 (95% CI 4.8 to 13.7) per million people whereas the incidence rate is 34.2 (95%CI 19.2 to 60.7) per million person-years [2]. As a capital cause of mortality in the elderly population with autoimmune skin diseases, the 1-year mortality rate of BP in the Middle Eastern population (26.9%) is in line with European (26.7%) and prominently higher than Asia (20.5%) and the United States (15.1%) [3]. At present, clinical

features, histopathology, direct/indirect immunofluorescence, and specific antibodies detections can all be used as diagnostic methods for BP.

The corticosteroids are crucial for treating BP, and topical or systemic corticosteroids can be administered according to the severity of BP. For moderate and severe BP, minocycline, nicotinamide, dapsone and other immunomodulators, or immunosuppressants (such as methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil) can also be used in combination on the basis of corticosteroids. In addition, there are intravenous immunoglobulin, plasma exchange, and other treatment methods [4]. Due to BP being the most common disease among elderly patients with a variety of basic diseases, high-dose corticosteroids and immunosuppressive measures undoubtedly increase the incidence of adverse events and medication safety issues,

leading to a markedly increase in the total mortality of BP. Therefore, the biologic agents with low safety issues and good therapeutic effects are expected to be used for treating BP. Currently, rituximab, omalizumab, and dupilumab are novel biologic agents used in the treatment of BP in recent years, but their application data in this disease are limited. Rituximab is a human-mouse chimeric monoclonal antibody against B lymphocyte CD20, which can specifically bind to the transmembrane antibody CD20 on the surface of B lymphocytes and clear peripheral B lymphocytes, and thus reducing the production of pathological antibody [5]. IgE plays an important role in the pathogenesis of BP. Omalizumab, as a recombinant humanized monoclonal IgG1 antibody targeting IgE, can specifically bind to IgE, reduce the level of free IgE, and prevent IgE from interacting with FcεRI, thereby significantly reducing inflammatory cell activation and inflammatory cascade, lowering eosinophil levels, reducing blister formation, and alleviating itch [5, 6]. Some studies suggest that patients who do not respond to rituximab and omalizumab often achieve remission after using dupilumab or in combination [7–15]. Dupilumab is a recombinant fully human IgG4 monoclonal antibody that selectively binds to human interleukin-4 receptor α(IL-4Rα) subunit and has the potential to inhibit both IL-4 and IL-13 signaling. It was theorized for autoimmune bullous diseases in 2019 and can significantly improve the treatment of BP patients who are resistant to corticosteroids, multiple immunosuppressants, immunomodulators, rituximab, and omazumab [16]. Hence, it can be seen that dupilumab will become a promising way for BP treatment.

Presently, the dupilumab has initially shown satisfactory efficacy in treating BP, but it is still in the initial stage of application. There is limited systematic data on the efficacy and safety of dupilumab, mainly in case series and case reports. Therefore, we decided to conduct this study by systematically reviewing existing reports on dupilumab and its treatment in BP patients to evaluate its safety and efficacy for treating BP.

2. Literature Analysis Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [17] and was registered with the PROSPERO registry (CRD42023404620). Articles on dupilumab for BP were searched in PubMed, Embase, Cochrane Library, and Web of Science databases from inception to March 10, 2023. The following search terms were used: (Pemphigoid, Bullous) OR (Bullous Pemphigoid) OR (Pemphigoid) OR (Pemphigoids)) AND ((Dupilumab) OR (SAR231893) OR (SAR-231893) OR (Dupixent) OR (REGN668) OR (REGN-668). In addition, the reviewers manually searched the relevant articles independently to avoid any additional articles that search engines might miss.

2.1. Eligibility Criteria. The diagnosis of BP should conform to the clinical characteristics of tension blisters and bullae usually appearing on an erythematous base, negative

Nikolsky's sign, mild or no mucosal damage, often accompanied by itch, and meet at least one of the following auxiliary diagnoses: (1) histopathology: subepidermal blisters with eosinophilic and/or neutrophilic inflammatory infiltration. (2) Direct immunofluorescence: the basement membrane area contains linear deposition of IgG and/or C3, and a few patients have linear deposition of IgA or IgE. (3) Indirect immunofluorescence: IgG autoantibodies that recognize the basement membranes are present in the serum of the patient and exhibit a linear distribution. (4) Specific antibody detection: elevated levels of anti-BP180 and/or anti-BP230 IgG antibodies can be detected in serum. There is no language or geographical restrictions on searching.

2.2. Outcomes. Primary outcomes: resolution outcomes of dupilumab treatment are as follows:

(1) Complete remission: Total resolution of BP lesions or well-controlled disease. The publications that used the terms "complete remission," "complete response," "complete control," "complete clearance," "complete resolution," or "symptom free" are included.

(2) Partial remission: Improvement but has not reached the total resolution of BP lesions. The publications that used the terms "partial remission," "partial response," "partial control," or "improvement" are included.

(3) No remission: No improvement in BP lesions. The publications that used the terms "no remission", "no response" or "no improvement" are included.

(4) Worsening: Exacerbation of BP lesions.

The secondary outcomes are as follows:

(1) Recurrence: Onset of new lesions during or after completion of dupilumab treatment. The publications that used the terms "relapsed," "flare," "recurrence of bullae," or "new blister" are included.

(2) Adverse events.

2.3. Study Selection and Data Extraction. Two reviewers (Ye and Ling) independently screened and cross-checked the retrieved articles, conducted preliminary screening by reading the title and abstract, and finally determined the articles to be included in the systematic review by reading the full text. Two reviewers (Ye and Ling) independently extracted the following information from included studies: first author, publication year, study design, number of patients, gender, age, BP duration, comorbidities, previous treatment, concomitant treatment, resolution outcome, recurrence, and adverse events. Any disagreement was resolved through discussion with a third reviewer (Chen).

2.4. Quality Assessment. Publications were graded according to the Oxford Centre for Evidence-Based Medicine 2009 Levels of Evidence [18]: (A) retrospective study and (B) case reports or case series.

2.5. *Statistical Analyses.* Descriptive statistics were used to analyze the data. Categorical variables are presented as numbers and percentages, and continuous variables are expressed as mean and range.

3. Literature Analysis Results

As is shown in Figure 1, a total of 174 publications were retrieved, of which 120 duplicated studies were excluded, 18 were excluded after reading the title and abstract, 10 were excluded after further full text reading, and 26 were finally included in a systematic review, with a total of 96 patients [7–15, 19–35]. The study mainly included 6 retrospective studies, 18 case reports, and 2 case series. Among the 96 patients, 41.7% ($n = 40/96$) were female and 58.3% ($n = 56/96$) were male, showing no statistical difference in gender. The median age was 74 years (range: 17–91 years) and median course of the disease was 12 months (range: 1–144 months). 28 patients were reported with BP IgG antibody information, of which 35.7% ($n = 10/28$) were positive for anti-BP180 IgG and anti-BP230 IgG, 7.1% ($n = 2/28$) were positive for anti-BP180 IgG, while anti-BP230 IgG was negative, 42.9% ($n = 12/28$) only reported positive for anti-BP180 IgG, and 14.3% ($n = 4/28$) only reported positive IgG antibodies without specific information. In addition, among 44 patients with serum total IgE data available, 97.7% ($n = 43/44$) had an increase in total IgE levels. In 15 patients, 80% ($n = 12/15$) had elevated eosinophil levels. Before dupilumab treatment, 65.6% ($n = 63/96$) of patients received systemic or topic steroids; 11.5% ($n = 11/96$), 5.2% ($n = 5/96$), 4.2% ($n = 4/96$), 3.1% ($n = 3/96$), 3.1% ($n = 3/96$), and 3.1% ($n = 3/96$) received immunosuppressants methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, cyclophosphamide, and *Tripterygium Glycosides* tablets, respectively; 3.1% ($n = 3/96$), 1.0% ($n = 1/96$), 17.7% ($n = 17/96$), and 7.3% ($n = 7/96$) received dapsone, thalidomide, doxycycline/minocycline, and nicotinamide, respectively; 7.3% ($n = 7/96$), 3.1% ($n = 3/96$), and 1.0% ($n = 1/96$) received intravenous immunoglobulin, antihistamines, and plasmapheresis, respectively; 4.2% ($n = 4/96$) and 7.3% ($n = 7/96$) received rituximab and omalizumab, respectively, but all failed. Due to some studies not providing information on the duration of previous treatment drugs and whether dupilumab was used alone or in combination, we are currently unable to better summarize the duration of previous treatments and the proportion of patients receiving dupilumab as a monotherapy or in combination. 28.1% ($n = 27/96$) did not receive any treatment before medication. Table 1 shows the baseline characteristics of the included articles and patients.

After dupilumab treatment, 66.7% ($n = 64/96$) of patients achieved complete remission, 25.0% ($n = 24/96$) had partial remission, 5.2% ($n = 5/96$) showed no remission, and no patients experienced deterioration. In addition, 1.0% ($n = 1/96$) and 2.0% ($n = 2/96$) patients stopped using dupilumab due to the adverse reactions and cost, respectively. The mean remission time was 4.5 months (range: 1–15 months). 46.2% ($n = 25/96$) of the patients were followed up with a median follow-up of 8 months (range: 4–12 months). Only 2 patients

relapsed at 8 and 7 months, respectively, and one of them showed significant improvement after re-treatment with dupilumab.

Information related to adverse events was reported in 10 articles with a total of 71 patients. No adverse events occurred in 83.1% ($n = 59/71$) of patients. Eosinophilia, deep venous thrombosis or pulmonary embolism, osteoporosis, poor cutaneous tolerance with "buming" sensation, herpes zoster, gastritis, pneumonia, and moderate pleural effusion due to Nocardia infection occurred in 5.6% ($n = 4/71$), 2.8% ($n = 2/71$), 1.4% ($n = 1/71$), 1.4% ($n = 1/71$), 1.4% ($n = 1/71$), 1.4% ($n = 1/71$), 1.4% ($n = 1/71$), and 1.4% ($n = 1/71$) of patients, respectively. No adverse events were reported in 26.0% ($n = 25/96$) of patients. There were 2 death events unrelated to treatment in 96 patients.

4. Discussion

A total of 96 patients were included in this systematic review, including 56 males and 40 females. The median age was 74 years (range: 17–91 years), consistent with the previously reported age of BP onset except for one 17-year-old girl with BP. BP is a relatively rare disease in children and adolescents. The treatment of pediatric BP usually requires corticosteroids and immunosuppressant, but it is worth noting that these drugs have significant side effects and therefore need to be used with great caution in pediatrics. In recent years, the dupilumab has emerged as a promising pediatric BP treatment, although there are more studies in older patients presently, and it is currently approved for widespread use in children with atopic dermatitis and has a high safety.

Before receiving dupilumab, 68 patients had received one or more traditional therapies, such as topical or systemic corticosteroids, doxycycline, minocycline, niacinamide, mycophenolate mofetil, dapsone, azathioprine, methotrexate, antihistamines, cyclosporine, cyclophosphamide, *Tripterygium Glycosides* tablets, thalidomide, plasmapheresis, and intravenous immunoglobulin, while all of which were ineffective. 11 were patients treated with other biological agents previously but showed poor efficacy. Among the four patients who received dupilumab treatment after failure of rituximab treatment, three had complete remission and one did not. Among the seven patients who failed omalizumab treatment, six achieved a complete response with dupilumab and one achieved a partial response. Different biological agents can achieve different clinical efficacy, indicating the complexity of autoantibody types and the extensive interindividual variation inherent in BP. Of note, one patient who received both omalizumab and dupilumab treatment achieved a complete response after 3 months of treatment, and no relapse was observed after 7 months of follow-up. For patients who did not have a response, whether to consider the combination of two or more biological agents need to be confirmed by large-scale clinical trials.

At present, the pathogenesis of BP is not completely clear, and some studies have shown that the autoimmune response driven by type 2 helper T cells (Th2) induces and maintains the occurrence of BP. Th2 cells can stimulate the proliferation of B cells and the production of autoantibodies
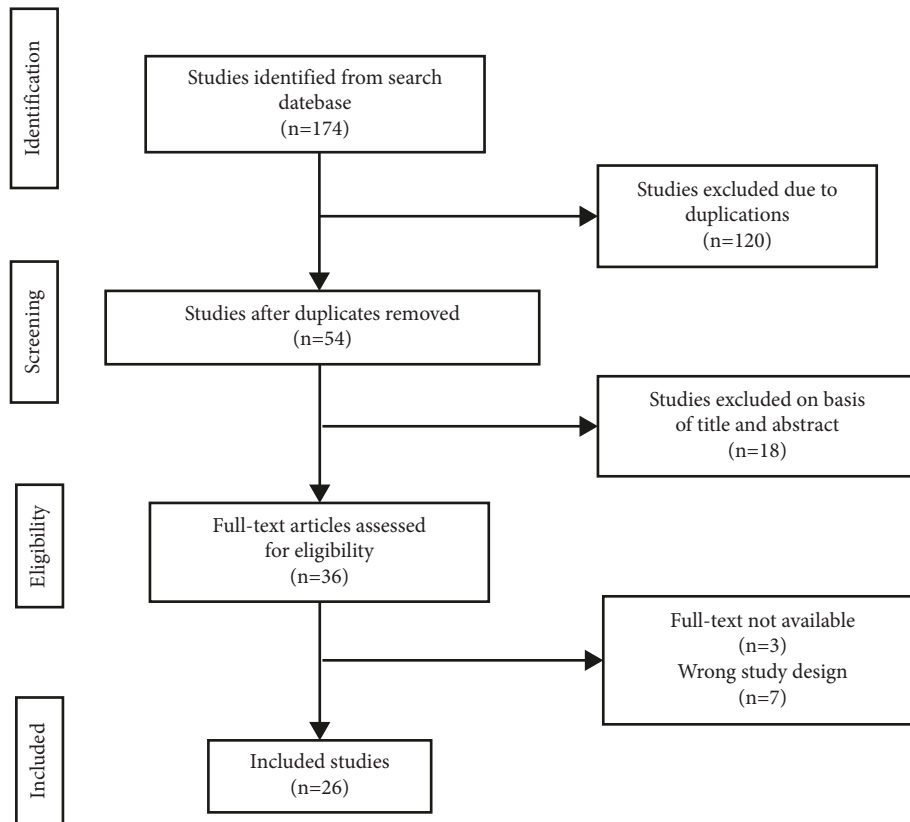
Figure 1: Flow diagram of the literature search and study selection.

and promote mast cell degranulation. Th2-related inflammatory cytokines and chemokines, such as IL-4, IL-5, IL-13, and CC motif chemokine ligand (CCL)-13 and CCL-18, are highly expressed in early BP lesions and serum [16, 36]. A study by Wanget al. [37] indicated that IL-13 concentration was elevated in blood circulation in BP patients. Another study suggests that the CCL-18 titers in the serum and blister fluid of BP patients were approximately 2 and 10 times higher than those of the healthy control group, respectively [38]. IL-4 and IL-13 are the main cytokines that drive Th2 response and can stimulate the growth and recruitment of eosinophils. Eosinophil infiltration is believed to contribute to the formation of blisters. IL-5 is also a key cytokine that regulates the maturation, survival, and recruitment of eosinophils and promotes eosinophils trafficking and accumulation into tissues, leading to separation inevitably occurred at the derma-epidermal junction. It was thought formerly that BP was mainly caused by circulating autoantibodies IgG targeting the structural proteins BP180 and BP230 in the epidermal basement membrane zone. BP230 is a 230 kDa intracellular protein and BP180 is a 180 kDa transmembrane protein. The extracellular noncollagenous 16A (NC16A) domain of BP180 contains immunodominant epitopes, and anti-NC16A IgG antibodies correlate with disease activity. Interestingly, the recent studies found that IgE autoantibodies with similar epitope specificity can be detected in serum and skin of BP patients as well and their titers reflect the severity of the disease, indicating that IgE may also play an important role in the pathogenesis of BP. IgE autoantibodies may regulate the function of Th2 cells and mediate Th1/Th2 balance drift towards Th2 by activating the IL-4/IL-13 pathway [16, 39]. BP is usually associated with an increase in peripheral blood eosinophils and serum IgE. Histopathology showed an increase in eosinophils infiltration in BP blister fluid, which is consistent with the statistical results of this work. In addition, some studies have demonstrated that eosinophilia is closely related to circulating total IgE levels. For BP patients with total IgE ≥ 400 IU/mL, the peripheral blood eosinophil counts relevant to the level of anti-BP180 IgE autoantibodies, which may be related to the expression of high-affinity IgE receptors FcεRI on eosinophils in BP patients [40, 41]. Th2 cells and related cytokines and chemokines can stimulate the production of eosinophils, thus exacerbating the condition, while eosinophils can promote the differentiation of T cells into Th2 cells through the IL-4/5/13 pathway, thereby forming a positive feedback to maintain high levels of inflammation in patients [16].

Apart from skin lesions, BP also exhibits intense itch. Research has confirmed that the amount of pruritus mediators in the skin lesions of BP patients were increased compared to healthy controls [42]. IL-31 is a cytokine released by Th2 cells and has been identified as one of the main sources of pruritus in BP patients [43]. By blocking the IL-4/IL-13 pathways, the Th2-driven inflammatory response can be inhibited, and the secretion of IL-31 and peripheral pruritus sensory neuron signals can be reduced, thereby improving pruritus symptoms.

TABLE 1: Baseline characteristics of the included articles and patients.

Author/ publish year	Study design	Number of patients	Gender	Age (years)/median (range)	Duration of BP (months)/median (range)	Patients' comorbidities	Previous treatment	Concomitant treatment	Resolution outcomes	Recurrence	Adverse events
Velin et al. [7] (2022)	A monocentric real-life study	8	4M, 4F	79.5 (70–87)	5.5 (1–29)	Chronic anemia (N=1); onset of hepatic fibrosis (N=1); Asthenia (N=1)	Superpotent TCs (N=8); oral steroids (N=3); OMZ (N=2)	Oral steroids (N=8); superpotent topical steroids (N=5)	Nontreatment-related deaths (N=2); complete response (N=3); partial response (N=1); stop for side-effect (N=1); No remission (N=1)	NR	Poor cutaneous tolerance with "buming" sensation (N=1)
Li W et al. [8] (2022)	Case report	1	M	89	NR	Atopic dermatitis; asthma; ulcerative colitis	OMZ	None	Resolution of eczema-like skin lesions and all blisters within 6 weeks	Remained symptom-free at 6 months	NR
Baffa et al. [9] (2023)	Case report	1	F	91	NR	Hypertensive chronic kidney failure;	Oral prednisone at a starting dose of 0.5 mg/kg/day and topical clobetasol propionate 0.05% ointment once daily; MPS (3 mg/kg/day) for 3 consecutive days; AZA 50 mg/day; RTX 1000 mg 2 weeks	NR	Complete resolution in pruritus and blisters within 2 months	NR	NR
Bur et al. [10] (2022)	Retrospective study	8	M	72 (58–87)	NR	Melanoma (N=7); anaplastic thyroid carcinoma (N=1); oropharyngeal SCC (N=2); cutaneous SCC (N=1); Merkel cell carcinoma (N=1); non-small-cell lung cancer (N=2); renal cell carcinoma (N=3); prostate cancer (N=1) urothelial carcinoma (N=2)	None (N=4); Doxycycline (N=3); MTX (N=1); OMZ (N=1)	TCs (N=8)	Disease remission (N=8)	NR	NR
Zhang et al. [11] (2023)	Retrospective study	7	3M, 4F	74 (63–88)	6 (1–36)	Hypertension (N=4); benign prostatic hyperplasia (N=2); diabetes (N=2); osteoporosis (N=1); after macular surgery (N=1); cirrhosis (N=1); myelodysplastic syndrome (N=1); hyperuricemia (N=1); inguinal hernia (N=1); pulmonary nodule (N=1)	None (N=5) tofacitinib (N=1) OMZ (N=1) glucocorticoid (N=1) CsA (N=1)	None (N=1); prednisolone (N=1); MPS (N=5)	Significant improvement within 8 weeks (N=7)	No recurrence for 9 months (range:6–12) (N=6) one patient relapsed at 28 weeks but the condition improved after being given again for q2w (N=1)	A moderate pleural effusion due to nocardia infection (N=1)

TABLE 1: Continued.

Author/ publish year	Study design	Number of patients	Gender	Age (years)/median (range)	Duration of BP (months)/median (range)	Patients' comorbidities	Previous treatment	Concomitant treatment	Resolution outcomes	Recurrence	Adverse events
Zhou et al. [12] (2022)	Case report	1	F	17	2	None	Intravenous methylprednisolone; oral prednisone; IVIG; RTX; plasmapheresis	Oral prednisone; IVIG; RTX; plasmapheresis	Pruritus improvement and absence of new lesion within 2 weeks	Complete blister resolution and undetectable BP-180 levels at a 4-month follow-up	NR
Seyed Jafari et al. [13] (2021)	Case report	1	M	70	24	Obesity; type 2 diabetes mellitus; arterial hypertension	TCs; dapsone; MTX; MMF; OMZ	TCs; MMF; OMZ	Complete remission (3 months)	Clinical remission (7-month-follow-up visit)	No adverse events
Abdat et al. [14] (2020)	Case series	13	8M, 5F	78 (53–91)	18 (1–60)	Hepatitis B core antibody (+) (N=1)	None (N=1); prednisone (N=8); IVIG (N=3); prednisolone (N=1); MTX, (N=4); doxycycline (N=4); mycophenolate (N=2) RTX (N=2); niacinamide (N=3) AZA (N=1)	None (N=6); MTX (N=3); prednisone (N=3); topical steroids (N=1)	Complete remission (N=7); partial response (N=4), No remission (N=2)	NR	No adverse events
Seidman et al. [15] (2019)	Case report	1	M	89	NR	Type 2 diabetes mellitus; thrush; corticosteroid myopathy	Doxycycline 100 mg twice daily; nicotinamide 500 mg twice daily; MMF 1000 mg twice daily (peak of 1500 mg twice daily); prednisone 10 mg daily; TCs; OMZ; various antihistamines	Prednisone 2.5 mg daily; MMF 500 mg twice daily; doxycycline 100 mg twice daily; nicotinamide 500 mg twice daily; topical clobetasol 0.05% cream; metformin	Itching improved within 2 weeks and complete resolution within 7 weeks	No recurrence for one year	NR
Lai et al. [19] (2022)	Case report	1	M	86	72	Type 2 diabetes mellitus; chronic kidney disease; triple-vessel coronary artery disease	AZA 50 mg daily	Systemic steroid treatment (MPS 4–32 mg/day); doxycycline (100 mg twice daily); topical clobetasol 0.05 ointment; systemic antihistamines	Complete resolution within 2 months	Complete resolution of the pruritus and heremained free of blisters and prurigo nodularis for 10 months	NR
Shan et al. [20] (2022)	Case report	1	M	32	18	Pulmonary tuberculosis	Oral corticosteroid	Prednisolone; isoniazid; rifampicin; ethambutol	Itching improved within 1 week; blisters resolved within 2 weeks; disease clearance (12 times injection)	NR	NR
Takamura et al. [21] (2022)	Case report	1	F	72	1.5	Type 2 diabetes mellitus	Minocycline; nicotinic acid amide	Dipeptidyl peptidase–4 inhibitors	Completely improvement of pruritus within 2 weeks and the skin blisters within 4 weeks	No recurrence at least 12 months	NR

TABLE 1: Continued.

Author/publish year	Study design	Number of patients	Gender	Age (years)/median (range)	Duration of BP (months)/median (range)	Patients' comorbidities	Previous treatment	Concomitant treatment	Resolution outcomes	Recurrence	Adverse events
Pop et al. [22] (2022)	Case report	1	F	59	NR	Cervical cancer	MPS (1 mg/kg/day divided twice daily); oral prednisone; oral doxycycline 100 mg twice daily; oral niacinamide 500 mg twice daily; oral dapsone 75 mg daily; topical bethamethasone diproprionate 0.05% ointment; triamcinolone 0.1% ointment	Oral doxycycline 100 mg twice daily; a prednisone course of 60 mg/day tapered down to 10 mg/day over 4 weeks	Disease clearance	Remained clear for an additional 6 months	NR
Bruni et al. [23] (2022)	Case report	1	M	76	18	Scalp nodular melanoma	Doxycycline 100 mg twice a day; MPS 40 mg/day for 10 days; TCs	MPS	Clinical remission within 6 months	NR	NR
Savoldy et al. [24] (2022)	Case report	1	M	78	NR	Type 2 diabetes mellitus; neurocognitive disease	Betamethasone dipropionate and triamcinolone 0.1% ointment; topical triamcinolone and lidocaine	Levemir; humalog; glimepiride; hydralazine; hydrocodone; terazosin; clonidine; carvedilol; ezetimibe; allopurinol; vitamin D; atorvastatin;	Disease improvement within 6 weeks	NR	No adverse events
Yang et al. [25] (2022)	Retrospective study	20	10M 10F	72 (54–86)	5 (3–12)	Interstitial lung disease (N=5); tumor (N=1); neurologic disorder (N=5); Cchronic renal insufficiency (N=3); cardiovascular disease (N=3); diabetes mellitus (N=4); hypertension (N=6)	Systemic therapy (N=3) none (N=17)	Low-dose MPS (N=20)	Complete remission (N=20)	NR	Eosinophilia (N=4); herpes zoster (N=1); deep venous thrombosis or pulmonary embolism (N=2); gastritis (N=1) pneumonia (N=1)
Wang et al. [26] (2022)	Case report	2	M	80 (72–88)	6.5 (1–12)	Type 2 diabetes (N=1) tuberculosis (N=1)	MPS (N=2); MTX (N=1)	MPS (N=2)	Disease improvement within 2 weeks (N=2)	NR	NR

TABLE 1: Continued.

Author/ publish year	Study design	Number of patients	Gender	Age (years)/median (range)	Duration of BP (months)/median (range)	Patients' comorbidities	Previous treatment	Concomitant treatment	Resolution outcomes	Recurrence	Adverse events
Xu et al. [27] (2023)	Case report	2	1M,1F	65.5 (53–78)	9 (6–12)	NR	Prednisone (N = 2); ebastine (N = 1); chlorphenamine maleate (N = 1); TCs (N = 1)	Prednisone (N = 2)	Significant improvement at first treatment and clinical remission at the 8-month (N = 1) significant improvement within 2 weeks (N = 1)	No recurrence during the 4-month follow-up (N = 1)	NRn(N = 1) No side effects of dupilumab during the 4-month follow-up (N = 1)
Saleh et al. [28] (2021)	Case report	1	M	80	3	NR	Topical triamcinolone ointment; prednisone 40 mg daily; doxycycline 100 mg twice daily; niacinamide 500 mg three times per day; MMF 1000 mg twice	NR	Marked improvement after 2 weeks, followed by complete clearance	NR	NR
Zhang et al. [29] (2021)	Case report	1	F	61	60	NR	MPS (0.5 mg/kg/day) taper; AZA 100 mg daily	MPS; topical steroids (clobetasol propionate 0.05% ointment twice/ day; AZA	Resolution of pruritus and skin blister within one month	Clinical remission at the 5-month follow-up visit	NR
Klepper et al. [30] (2021)	Case report	1	F	79	NR	Melanoma	Triamcinolone 0.1% ointment; clobetasol 0.05% ointment; 100 mg of doxycycline twice daily; 180 mg of fexofenadine daily; oral dapsone; emollients; prednisone	NR	Complete remission of pruritus and BP lesion within 4 weeks	NR	NR
Zhang et al. [31] (2021)	Retrospective study	8	3M, 5F	64.5 (45.5–71.7 5)	2 (1.25– 49.5)	Cardiovascular disease (N = 3); cancers (N = 2); neurologic disorders (N = 1); hyperlipidemia (N = 3)	NR	MPS (N = 8) (0.6 mg/kg/day) AZA(N = 8) (2 mg/ kg/day)	Complete remission (N = 5) partial remission (N = 1) no remission (N = 2)	One patient relapsed within 32 weeks	Osteoporosis (N = 1)
Liu et al. [32] (2021)	Case series	3	1M, 2F	54 (50–68)	17 (3–36)	Psychiatric disorder (N = 1); HBV + (N = 2); hypertension (N = 1); type 2 diabetes mellitus (N = 1); arrhythmias with sustained atrial fibrillation (N = 1); stroke (N = 1)	MPS 80 mg/d (N = 2); prednisone (N = 1); CsA (N = 1); CTX (N = 2); IVIG (N = 2); dexamethasone (N = 1); MTX (N = 1)	MPS (N = 2); MTX (N = 1); CsA (N = 1); IVIG (N = 1); CTX (N = 1)	Disease clearance within 1 month (N = 1); disease improvement within 1 week (N = 1) pruritus improved but not the skin lesions (after three injections, N = 1)	NR	No adverse events
Singh et al. [33] (2020)	Case report	1	F	83	2	Chronic lymphocytic lymphoma; severe congestive heart failure; Alzheimer's dementia; latent tuberculosis	Prednisone	NR	Itch improved and no new bullae appeared within 3 weeks; complete resolution of disease within 15 weeks	NR	NR

TABLE 1: Continued.

| Author/ publish year	Study design	Number of patients	Gender	Age (years)/median (range)	Duration of BP (months)/median (range)	Patients' comorbidities	Previous treatment	Concomitant treatment	Resolution outcomes	Recurrence	Adverse events
Kaye et al. [34] (2018)	Case report	1	M	80 s	1.5	Mycobacterium tuberculosis and hepatitis B core antibody (+)	Prednisone and immunomodulatory	NR	Itching improved within 1 week; resolution of all blisters after 3 months	No recurrence at least 10 months	NR
Liang et al. [35] (2023)	Retrospective study	9	7M, 2F	68 (42–89)	6 (1.5–144)	Mycobacterium tuberculosis ($N=5$); obsolete pulmonary tuberculosis ($N=2$); asthma ($N=1$); thyroid disorders ($N=5$); sleep disorders ($N=1$); hypertension ($N=6$); cardiovascular disease ($N=4$) type 2 diabetes mellitus ($N=2$); old myocardial infarction ($N=1$); hepatitis B core antibody (+) ($N=1$); osteoporosis ($N=3$); COPD ($N=1$); yypoproteinemia ($N=1$) bronchial stenosis ($N=1$); scoliosis ($N=1$); hernia cholelithiasis ($N=1$); cholecystitis ($N=1$); hydrocele ($N=1$); skin infection ($N=2$); arthritis ($N=1$); elevated PSA levels ($N=1$; old silent lacunar infarcts ($N=1$); diabetic nephropathy ($N=1$); old cerebral infarction ($N=1$); chronic anemia ($N=1$; Alzheimer's disease ($N=1$); chronic kidney disease ($N=1$) epilepsy ($N=1$)	TCs ($N=9$) systemic steroids ($N=5$) CsA ($N=1$) *Tripterygium glycosides tablets ($N=3$); minocycline ($N=4$); thalidomide ($N=1$); IVIG ($N=1$); CTX ($N=1$)	TCs ($N=9$); systemic steroids ($N=8$); CsA ($N=1$); *Tripterygium glycosides tablets ($N=7$); minocycline ($N=8$); thalidomide ($N=1$); CTX ($N=1$)	Complete remission ($N=6$); partial response ($N=1$); lesions improved within 4 weeks discontinued due to cost ($N=2$)	NR	No significant adverse effects
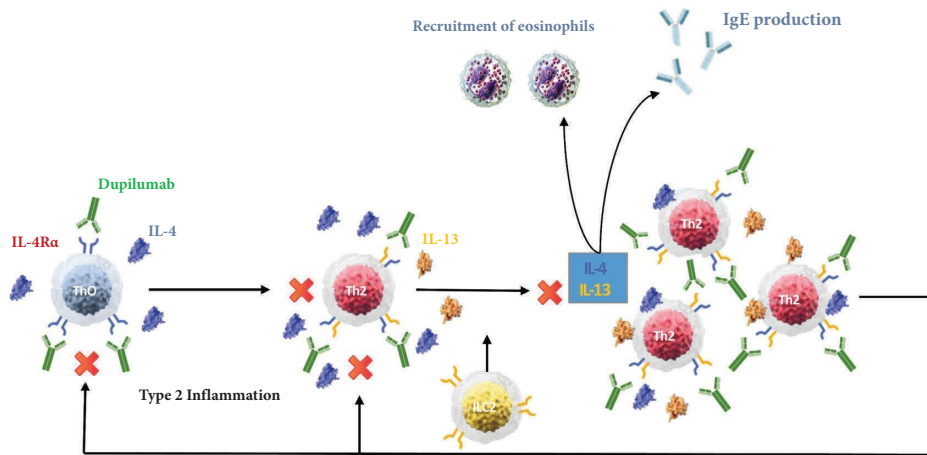
Figure 2: Possible mechanism diagram of dupilumab in treating BP.

The IL-4/IL-13 pathway plays a major role in the pathogenesis of BP, laying a theoretical foundation for the treatment with dupilumab. At present, the mechanism of dupilumab in the treatment of BP has not been fully clarified. Figure 2 shows the possible mechanism of dupilumab in treating BP. Dupilumab is a recombinant human monoclonal antibody that can specifically bind to IL-4Rα subunits, coreceptor of IL-4 and IL-13, block downstream signal transduction of IL-4 and IL-13, inhibit B cell proliferation, eosinophil chemotaxis, and Th2 chemokine expression, thereby alleviating Th2-cell-mediated diseases [44]. Dupilumab may be a viable treatment option for BP because it is an IL-4Rα antagonist and has additional IL-31 inhibitory properties [22, 45]. In our report, dupilumab has achieved good clinical efficacy in BP with complete response rate of 66.7%, partial response rate of 25%, and total effective rate of 91.7%. Although dupilumab has achieved good clinical efficacy, not all BP patients have responded well to dupilumab treatment. What kind of BP patients have a good effect after treatment with dupilumab, or what kind of indicators can suggest that the patient can choose dupilumab, which is still a gap that needs to be filled in current research. At present, a retrospective cohort study may provide us with a reference that patients with serum anti-BP180 antibody levels ≥50 RU/mL and female may have better responses to dupilumab [46]. Therefore, in the following work, it is hoped that there will be large-scale clinical randomized controlled trials and high-quality systematic review to address this issue.

The most common adverse effect of dupilumab in this report is a transient increase in peripheral blood eosinophils, and its mechanism is not fully understood, but several studies have proposed some possible explanations. IL-4 and IL-13 regulate eosinophilic chemokines and induce the expression of vascular cell adhesion molecule 1 in endothelial cells, thereby promoting the entry of eosinophils into inflammatory site through vascular endothelial cells [47, 48]. After dupilumab treatment, the IL-4 and IL-13 levels in peripheral blood were downregulated, which mainly inhibited the migration and infiltration of blood eosinophils into skin tissues, but could not directly target the IL-5 pathway to regulate the maturation, proliferation, and

circulation of bone marrow eosinophils. As the main eosinophil chemotactic agent, IL-5 can promote the release of various inflammatory mediators and proteases from eosinophils into lesions, leading to the formation of blisters.

In addition, IL-5 can promote eosinophil passage through the basement membrane and induce superoxide anion to enhance the release of eosinophilic plasma particles through synergistic effects with eosinophilic chemokines. As a result, the number of eosinophils in the circulation may increase to some extent. However, interfering with the IL-4/IL-13 pathway also reduces the production of eosinophils, which may partially offset the dupilumab-associated eosinophilia, which explains why the accumulation of eosinophils in the blood is transient [49]. As for other adverse events, such as osteoporosis, poor cutaneous tolerance with "buming" sensation, herpes zoster, and gastritis, reported in the included articles [7, 25, 31], the incidence rate is extremely low, individual differences cannot be excluded, nor can it be clearly confirmed that their occurrence is related to the use of dupilumab, which needs further research. We believe that with the widespread application of dupilumab in the treatment of BP, the situation and mechanism of adverse reactions will gradually become clearer. In addition, some newly published articles have reported that there were no adverse reactions or only injection-related adverse reactions during the treatment of BP with dupilumab [50–53]. Therefore, we can preliminarily conclude that the treatment of BP with dupilumab is generally safe. This is consistent with the conclusion of another review article [54].

5. Conclusion

This systematic review comprehensively summarizes and analyzes reports of dupilumab in BP treatment. The results indicate that dupilumab is a promising treatment for BP with high clinical benefit associated with a low recurrence rate, adverse event rate, and mortality. Due to the limitations of small sample size, study design, and publication bias in this systematic review, large-scale randomized clinical trials are needed in the future to further confirm the safety and efficacy of dupilumab in BP.

Data Availability

No data were used to support the findings of this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Shengzhen Ye and Mingling Chen provided the study concept and design. Shengzhen Ye and Guihua Ling obtained and statistically analyzed the data. All authors interpreted the data, drafted the manuscript, and critically revised the manuscript.

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