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REVIEW ARTICLE

Targeting interleukin 4 and interleukin 13: a novel therapeutic approach in bullous pemphigoid

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ABSTRACT

Aim: Bullous pemphigoid (BP) is an organ-specific autoimmune bullous disease characterized by autoantibodies that target the cellular adhesion molecules BP180 and BP230. Both immunoglobulin (Ig)G and IgE are involved in the induction of subepidermal blisters. Specifically, IgE autoantibodies are presumed to be responsible for the pruritic and erythematous features of BP. Histologically, eosinophil infiltration is a prominent feature in BP. Eosinophils and IgE are mostly associated with the Th2 immune response. Th2 cytokines, particularly interleukin (IL)-4 and IL-13, are presumed to contribute to the pathology of BP. The aim of this review is to discuss the role of IL-4/13 in the pathogenesis of BP and the potential of using IL-4/13 antagonists for treatment.

Methods: After searching in PubMed and Web of Science databases using 'bullous pemphigoid', 'interleukin-4/13', and 'dupilumab' as keywords, studies related was compiled and examined.

Results: Overall, IgE, eosinophils, IL-4, and IL-13 may interact with each other in the pathogenesis of BP; these potential interactions provide clues concerning targets for molecular treatment.

Conclusion: Anti-IL-4/13 treatment has been experimentally used in patients with BP, with satisfactory outcomes and few side effects. However, before this novel therapy can be approved for regular usage, further studies are needed concerning the long-term safety and systemic usage of IL-4/13 monoclonal antibody treatment in BP.

KEY MESSAGES

- BP is an autoimmune skin disease with Th2-mediated autoimmune response involvement.
- As typical Th2 cytokines, IL-4 and IL-13 may contribute to the pathogenesis of BP in multiple ways, such as promoting Th2 cell polarization, driving the immunoglobulin class switching, recruiting eosinophils and basophils, and inducing pruritus.
- As a promising therapeutic approach for BP, IL-4/13 antagonists have shown satisfactory outcomes in preliminary clinical studies.

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Bullous pemphigoid; Th2 cells; interleukin-4; interleukin-13; dupilumab; monoclonal antibody therapy

Introduction

Bullous pemphigoid (BP) is an autoimmune bullous skin disease mediated by pathogenic autoantibodies that target the hemidesmosome proteins BP antigen 180 (BP180) and BP antigen 230 (BP230) [1–3]. Clinically, BP is characterized by large, tense blisters and erythema, and it mostly affects senior adults [4]. Histologically, BP presents with subepidermal blisters with neutrophil and eosinophil infiltration. BP180 is a transmembrane glycoprotein with a globular cytoplasmic N-terminal domain, whereas BP230 is an intracellular constituent of hemidesmosome plaques [1,2]. Most patients with BP have circulating immunoglobulin (Ig) G autoantibodies that target BP180, particularly in non-collagenous domain 16A (NC16A), which is the immunodominant region recognized by autoreactive T and B cells [5]. In BP, T cell responds with both T helper 1 (Th1) and T helper 2 (Th2) cells. Thus, in patient serum, both Th2-mediated IgG4 and Th1-mediated IgG1 autoantibodies are present [6]. However, the presence of IgG autoantibodies does not explain all of the clinical features involved in BP. Factors other than IgG autoantibodies may also contribute to the pathogenesis of cutaneous inflammation in BP, such as T-helper autoreactive lymphocytes, cytokines, IgE, and eosinophils [7,8]. Whereas interleukin-4 (IL-4) and interleukin-13 (IL-13) are two key cytokines

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in Th2 autoimmune response, IL-4 and IL-13 are presumed to contribute to the pathogenesis of BP.

Current treatment options for BP are primarily corticosteroids, with or without immunosuppressive drugs, such as methotrexate, azathioprine, and mycophenolate mofetil. The combination of such treatments can have life-threatening effects, including severe infections, osteoporosis, and metabolic disorders [9]. Therefore, new therapies with fewer side effects are needed. Atopic dermatitis (AD) is a common pruritic dermatosis with a Th2-dominant immune response [10]. AD is characterized by the overexpression of Th2 cytokines, such as IL-4 and IL-13. IL-4/13 antagonists, such as dupilumab have yielded satisfactory outcomes in the treatment of AD, with few side effects [11]. Because of the important role of Th2 immune response in BP and the possible contribution of IL-4/13 in maintaining Th2 immune response, IL-4/13 antagonists might yield similar outcomes in the treatment of BP. There have already been abundant case reports and case series studying the use of dupilumab in BP with promising results [12–33] (Table 1). However, the mechanisms underlying the therapeutic effects have not been fully revealed.

Our review briefly summarizes the autoimmune mechanisms involved in BP, the roles of IL-4 and IL-13 in immune disorders, and the roles of IL-4 and IL-13 in the pathophysiology of BP. Additionally, we describe current anti-IL-4/13 strategies and their potential side effects in the treatment of BP.

Bullous pemphigoid and immune response

BP is regarded as an IgG-mediated disease. In patients with BP, IgG1, and IgG4 are the predominant circulating subtypes of IgG [34]. IL-4 reportedly can interfere with IgG isotype switching by promoting the production of IgG4 [35]. When IgG1 autoantibodies bind to their targets, complement activation is induced. Complement fragments (e.g. C3a and C5a) then recruit neutrophils and eosinophils to BP lesions [6]. Subsequently, neutrophils and eosinophils release proteolytic enzymes, such as matrix metallopeptidase-9 and neutrophil elastase, which destroy the linkage between dermis and epidermis and result in subepidermal blistering [6]. In contrast to IgG1, IgG4 autoantibodies have a more complex function in BP; they may promote blister formation in a complement-independent manner [36]. Patients with dual IgG1 and IgG4 responses to BP180 often exhibit severe skin evolvement [37]. Mihai et al. suggested that, although IgG4 does not fix complement, it contributes to the formation of blisters by activating leukocytes and inducing dermal-epidermal separation [38]. However, another study showed that IgG4 autoantibodies may play an immunoregulatory role in BP by inhibiting the binding of IgG1 and IgG3 to the NC16A region, thereby attenuating complement activation and blister formation [39].

In addition to IgG autoantibodies, IgE autoantibodies are associated with BP [40]. Whereas the pathogenic role of IgE in allergic disorders is well-known, the potential role of IgE in BP is also under research. Similar to IgG, IgE BP180 NC16A-specific autoantibodies have been identified [41,42]. Moreover, the levels of IgE autoantibodies targeting NC16A correspond to BP severity and activity [41,43].

IgE has two receptors, FcεRI and FcεRII (CD23). FcεRI is a high-affinity receptor, primarily distributed on mast cells and basophils; CD23 is a low-affinity receptor, found mainly on mature B cells and eosinophils. Both receptors are involved in stimulating the Th2 response [44]. The binding of IgE autoantibodies to mast cells and basophils induces degranulation, which is responsible for eosinophil infiltration in the BP lesions [45]. Mast cells express high levels of FcεRI for eosinophils recruitment and can produce major regulating cytokines for eosinophils like IL-5 [46]. Consistent with the distribution of receptors, Freire et al. reported that IgE autoantibodies could not only be detected in the serum of patients with BP but also in the basement membrane zone and on the surface of mast cells and eosinophils, which indicates the interaction between IgE and cells with high-affinity receptors [45]. Furthermore, there is evidence that both FcεR-dependent and -independent immune reactions promote blister development in BP, and that IgE is involved in the onset of BP [40,47–50]. For *in vivo* studies, Lin et al. found that the severity of the disease depends on IgE dose and is related to the degree of eosinophil infiltration in lesions [51]. In addition to inducing blister formation, the administration of IgE autoantibodies can also recapitulate similar symptoms, such as pruritus, erythema, and eosinophilia, which are absent in sole IgG-based mouse models [40,47]. This finding may explain why patients with BP often exhibit pruritic erythema and eosinophilic infiltration.

Eosinophilia is a typical pathological feature of BP. The numbers of eosinophils and secretory granules (e.g. eosinophil cationic protein) in serum are reportedly correlated with the severity of BP [52,53]. Eosinophils can promote the pathogenesis of blistering in BP by releasing proteolytic enzymes and producing extracellular traps [35,54]. Pruritus in BP could last for months or remain the only symptom, which is difficult to control [55]. The mechanism underlying the onset

Table 1. Case reports and studies of BP patients treated with dupilumab.

	Year of publication	Number of patients	Sex	Age (years)	Patients' comorbidities	Concomitant medication	Systemic BP medication before dupilumab (overall)
Cao et al. [28]	2022	26	15 M, 18 F, 3 Not Reported	74.3 Mean	Not reported	Not reported	Corticosteroids (*N* = 24/36); Methotrexate (*N* = 8/36); Mycophenolate Mofetil (*N* = 5/36); Azathioprine (*N* = 2/36); Cyclosporine (*N* = 1/36); Cyclophosphamide (*N* = 1/36); Dapsone (*N* = 1/36); Doxycycline (*N* = 6/36); Nicotinamide (*N* = 5/36); Intravenous immunoglobulin (*N* = 5/36); Antihistamines (*N* = 1/36); Rituximab (*N* = 2/36); Omalizumab (*N* = 5/36)
Velin et al. [29]	2022	8	4 M, 4 F	79.5 Mean	Not reported	Not reported	Topical corticosteroids (*N* = 8); Systemic corticosteroids (*N* = 1); Methotrexate (*N* = 3); Omalizumab (*N* = 2)
Yang et al. [19]	2022	20 in dupilumab and methylprednisolone group (dupilumab group); 20 in methylprednisolone alone group (control group)	10 M and 10 F in dupilumab group; 8 M and 12 F in control group	72 Median in both group	Hypertension (n1 = 6) (n2 = 7); Cardiovascular disease (n1 = 3) (n2 = 4); Diabetes mellitus (n1 = 4) (n2 = 3); Chronic renal insufficiency (n1 = 3) (n2 = 3); Neurologic disorder (n1 = 5) (n2 = 6); Interstitial lung disease (n1 = 5) (n2 = 4); Tumor (n1 = 1) (n2 = 3)	Not reported	3 patients with dupilumab had previously undergone systemic therapy; 37 patients were newly diagnosed and received no prior treatment
Takamura and Teraki [30]	2022	1	F	72	Diabetes mellitus	Dipeptidyl peptidase-4 inhibitors	Minocycline and nicotinic acid amide; Patients refuse treatment with oral corticosteroids
Pop et al. [21]	2022	1	F	59	Cervical cancer	Pembrolizumab	Methylprednisolone, prednisone, doxycycline, niacinamide, dapsone, and topical corticosteroids
Wang et al. [17]	2022	1	M	72	Type 2 diabetes mellitus	Not reported	Methylprednisolone and methotrexate
Wang et al. [17]	2022	1	M	88	Tuberculosis	Not reported	Methylprednisolone at high dose
Shan and Zuo [20]	2022	1	M	32	Tuberculosis	Isoniazid, rifampicin, and ethambutol	Corticosteroid 15 mg daily (later increased to 35 mg daily)
Jendoubi et al. [22]	2022	1	F	76	Hypertension, diabetes, obesity, and atrial fibrillation	Not reported	Topical corticosteroids
Bruni et al. [23]	2022	1	M	76	Melanoma	Nivolumab	Systemic and topical corticosteroids, and doxycycline
Li et al. [18]	2022	1	M	85	Asthma and ulcerative colitis	No need for drugs	Topical corticosteroids, tofacitinib, antihistamines, and omalizumab,
Valenti et al. [33]	2022	1	M	63	Atopic dermatitis and allergic rhino-conjunctivitis	Not reported	Methylprednisolone, azathioprine, dapsone, and colchicine
Bal et al. [31]	2022	1	M	74	Diabetes mellitus and hypertension	Metoprolol	Systemic and topical corticosteroids
Zhang et al. [14]	2021	8	3 M, 5 F	64.50 Median	Cardiovascular disease (*N* = 3); Neurologic disorders (*N* = 1); Hyperlipidemia (*N* = 3); Cancers (*N* = 2)	Not reported	Not reported

Response to medication before dupilumab	Disease duration before dupilumab initiation (months)	Dosage of dupilumab	Concurrent therapies with dupilumab	Response to dupilumab	Last follow-up condition
Failed to control disease	19.2 Average	Not mentioned	Corticosteroids ($N=26/36$); Methotrexate ($N=3/36$); Mycophenolate mofetil ($N=2/36$); Azathioprine ($N=9/36$); Cyclosporine ($N=0/36$); Cyclophosphamide ($N=1/36$); Dapsone ($N=0/36$); Doxycycline ($N=2/36$); Nicotinamide ($N=1/36$); Intravenous immunoglobulin ($N=0/36$); Antihistamines ($N=0/36$); Omalizumab ($N=1/36$); None ($N=3/36$); Not reported ($N=1/36$)	Complete remission ($N=86/122$); Partial remission ($N=29/122$); No remission ($N=6/122$); Deteriorated ($N=1/122$); Average remission time: 5.7 months	Mean follow-up time: 21.9 months; Recurred ($N=25/122$); Did not recur ($N=86/122$); Did not report ($N=4/122$)
Unresponsive	17.2 Mean	600 mg SC initially; 300 mg Q2W	Topical corticosteroids ($N=7$); Systemic corticosteroids ($N=5$)	Complete response ($N=3$); Partial response ($N=1$); Poor response ($N=1$); Non-treatment-related deaths ($N=2$); Intolerance with burning sensation ($N=1$)	/
The 3 patients reached complete remission off therapy, but relapsed without treatment	5 Median in both group	600 mg SC initially; 300 mg Q2W	Equivalent dose of methylprednisolone at <0.4 mg/kg/day for patients in dupilumab group; Equivalent dose of methylprednisolone at 0.4 mg/kg/day in moderate patients or at 0.6–0.8 mg/kg/day in patients with extensive disease in control group	Shorter time to reach disease control in the dupilumab group than the control group (14 *vs.* 19 days, $p=0.043$); Lower control dose and cumulative dosage of methylprednisolone in the dupilumab group than the control group (24.6 *vs.* 48.8 mg, 376.8 *vs.* 985.6 mg, both $p<0.01$); Less adverse events in the dupilumab group	/
No improvement	1.5	600 mg SC initially; 300 mg Q2W	Not reported	Complete improvement of pruritus within 2 weeks; Complete improvement of skin blisters within 4 weeks; Anti-BP180 antibodies became negative at 7 months	No recurrence of BP for at least 12 months
Numerous flares of BP	12	300 mg Q2W	Steroid 60 mg daily (0.75 mg/kg/day) tapered down to 5 mg daily after 2 months;	Cessation of new BP lesions after 2 months; Relapsed after missed 4 doses of dupilumab at month 5; Re-initiation of dupilumab, doxycycline 100 mg twice daily, and prednisone 60 mg daily (tapered down to 10 mg/day over 4 weeks) reached disease clearance	Remained clear for an additional 6 months
Absence of improvement	Not reported	300 mg SC twice	Not reported	Significant improvement of pruritus the next day; Improvement of skin lesions after 2 weeks	Not reported
Absence of skin lesions improvement	12	300 mg SC twice	Not reported	Significant improvement of skin lesions after 2 weeks	Not reported
Two flares of disease and later diagnosed of pulmonary tuberculosis	18	600 mg SC initially; 300 mg Q2W	Prednisolone	Improvement of pruritus within 1 week; Cessation of new vesicles within 1 week; Clearance of vesicles within 2 weeks	Discontinued of prednisolone; Remained stable after treated with dupilumab for 12 times
Flare of disease during tapering of topical corticosteroids	Not reported	600 mg SC initially; 300 mg Q2W	Not reported	Clearance of pruritus and lesions in 4 months	No recurrence for at least 6 months
Flare of disease during tapering of corticosteroids	Not reported	300 mg Q2W	Methylprednisolone 20 mg daily	Significant clinical improvement after 2 months; Cessation of new blisters within 4 months; Clearance of BP lesions in 6 months	/
Absence of improvement	2	600 mg SC initially; 300 mg Q2W	Not reported	Improvement of pruritus within 1 week; Clearance of BP lesion after 6 weeks	No recurrence for at least 6 months
Unsatisfactory response	6	600 mg SC initially; 300 mg Q2W	Not reported	Remarkable improvement of skin lesions after 1 month	In clinical remission at month 6
Minimal improvement	5–6	600 mg SC initially; 300 mg Q2W	Not reported	Improvement of pruritus within 1–2 weeks; Clearance of BP lesion in 4 weeks	No flares or recurrence for at least 12 months
Not reported	2 Median	600 mg SC initially; 300 mg Q2W	Methylprednisolone (0.6 mg/kg/day) and azathioprine (2 mg/kg/day)	Median time of cessation of new BP lesions: 8 days; 62.5% of patients reached complete remission	/

Klepper and Robinson [26]	2021	1	F	79	Melanoma	Nivolumab, levothyroxine, hydrochlorothiazide/losartan, atorvastatin	Doxycycline, fexofenadine, dapsone, and topical steroids
Seyed Jafari et al. [15]	2021	1	M	70	Obesity, type 2 diabetes mellitus, and hypertension	Not reported	Topical corticosteroids, dapsone, methotrexate, mycophenolate-mofetil, and omalizumab
Zhang et al. [24]	2021	1	F	61	Not reported	Not reported	Methylprednisolone and azathioprine
Saleh et al. [25]	2021	1	M	80	Not reported	Not reported	Prednisone, doxycycline, niacinamide, and mycophenolate mofetil
Liu et al. [32]	2021	1	F	54	Psychiatric disorder	Not reported	Methylprednisolone, dexamethasone, intravenous immunoglobulin, cyclophosphamide and topical corticosteroids
Liu et al. [32]	2021	1	M	50	HBsAg (+) with high copies of HBV	Not reported	Methylprednisolone, intravenous immunoglobulin, methotrexate, cyclosporine and topical corticosteroids
Liu et al. [32]	2021	1	F	68	Hypertension, type 2 diabetes mellitus, stroke, arrhythmias with sustained atrial fibrillation, and HBsAg (+) with high copies of HBV	Not reported	Prednisone, cyclophosphamide, topical corticosteroids
Abdat et al. [13]	2020	13	8 M, 5 F	76.8 Average	Not reported	Not reported	None ($N=1$); Prednisone ($N=3$); Methotrexate ($N=1$); Doxycycline ($N=1$); Prednisone and methotrexate ($N=2$); Prednisone, doxycycline, and niacinamide ($N=1$); Prednisolone, methotrexate, intravenous immunoglobulin ($N=1$); Prednisone, mycophenolate, rituximab, and intravenous immunoglobulin ($N=1$); Prednisone, mycophenolate, doxycycline, and niacinamide ($N=1$); Rituximab, intravenous immunoglobulin, doxycycline, nicotinamide, and azathioprine ($N=1$);
Seidman et al. [27]	2019	1	M	89	Type 2 diabetes mellitus	Metformin	Prednisone, doxycycline, nicotinamide, mycophenolate mofetil, and omalizumab
Kaye et al. [16]	2018	1	M	80s	Mycobacterium tuberculosis and hepatitis B core laboratory positivities	Not reported	Prednisone

n1: dupilumab and methylprednisolone group = dupilumab group; n2: methylprednisolone group = control group.

(*Continued*)

Intolerance of prednisone	Not reported	600 mg SC initially; 300 mg Q2W	Not reported	Clearance of pruritus after 4 weeks; Cessation of new blisters within 4 weeks;	Maintain clearance after 24 doses of dupilumab
Constant mild itch with transient prurigo-like lesions	24	600 mg SC initially; 300 mg Q2W	Mycophenolate-mofetil, omalizumab and topical steroids	Clearance of pruritus and cessation of new BP lesions within 3 months	In clinical remission at month 7; Stopped mycophenolate-mofetil and topical corticosteroids at month 7
Two flares of disease during tapering of methylprednisolone and 3 months of azathioprine failed to control disease	Not reported	600 mg SC initially; 300 mg QW	Methylprednisolone, azathioprine, and topical steroids	Clearance of pruritus within 1 month; Cessation of new BP lesions within 1 month	In clinical remission at month 5; No flare was observed during tapering of methylprednisolone; Stopped azathioprine at month 5
Flare of disease during tapering of prednisolone; Intolerance of mycophenolate mofetil	Not reported	600 mg SC initially; 300 mg Q2W	Prednisone, doxycycline	Significant improvement in BP lesions in 2 weeks; Reached disease clearance	Remain disease clearance on dupilumab and doxycycline
Poor response; psychosis progression	17	600 mg SC initially; 300 mg Q2W for twice	Methylprednisolone, CTX, and Topical corticosteroids,	Disease clearance within 1 month	No flare was observed during tapering of methylprednisolone for 12 weeks
Poor response	3	600 mg SC once	Methylprednisolone, methotrexate, cyclosporine and topical corticosteroids	Disease controlled within 1 week	No flare was observed during tapering of methylprednisolone over 2 months
Poor response; Developed gastric ulcer	>36	600 mg SC initially; 300 mg Q2W for twice	Topical corticosteroids	Improvement of pruritus within 1 week and maintained for 2 months; No improvement in bulla	/
Failed to control disease	28.8 Average	600 mg SC initially ($N=13$); 300 mg Q2W ($N=10$); 300 mg QW ($N=2$); every 12 days ($N=1$)	None ($N=6$), Prednisone ($N=3$), Methotrexate ($N=3$), Intralesional and topical steroids ($N=1$)	Absence of both bullae and pruritus ($N=7$); Resolved bullae with residual pruritus ($N=10$); Objective improvement of pruritus ($N=11$); Complete resolution of pruritus ($N=7$); Improvement in pruritus with persistent bulla ($N=1$); No improvement in pruritus or bulla ($N=1$)	/
Flare of disease during tapering of prednisone; Flare of disease 6 months after starting omalizumab	24	Dupilumab every other week (dosage not reported)	Prednisone 2.5 mg daily mycophenolate mofetil 500 mg twice daily, doxycycline 100 mg twice daily, nicotinamide 500 mg twice daily and topical steroids	Improvement of pruritus within 2 weeks; Complete BP lesions resolution after 7 weeks	Continued benefit from dupilumab at 1 year
Two flares of disease during tapering of prednisone	1.5	600 mg SC initially; 300 mg QW	Not reported	Improvement in pruritus within a week; Clearance of all blisters after 3 months; Undetectable levels of BP180 and BP230 antibodies after 3 months	Remained clear of lesions after 10 months of dupilumab monotherapy

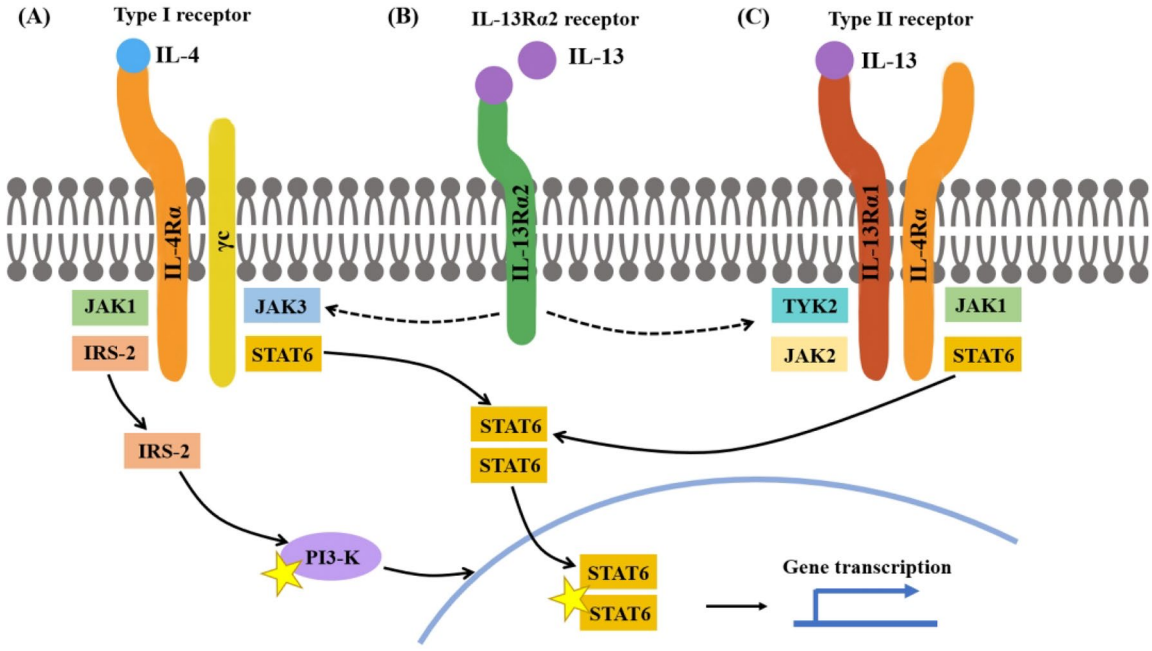

Figure 1. IL-4 and IL-13 receptor structure IL-4 can bind to both type I and type II receptors. (A) Type I receptors consist of IL-4Rα and γc, whereas type II receptors consist of IL-4Rα and IL-13Rα1. When IL-4 binds to a type I receptor, Janus kinase (JAK) 1 and JAK3 are activated; both can induce tyrosine phosphorylation of the type I receptor intracellular domain, forming docking sites for downstream signaling molecules, such as signal transducer and activator of transcription (STAT) 6 and insulin receptor substrate-2 (IRS-2). Homodimers of STAT6 then translocate to the nucleus to facilitate transcription of IL-4- and IL-13-dependent genes. IRS-2 can activate signaling molecules, such as PI3K to induce gene transcription. (B) IL-13 binds to IL-13Rα2 with greater affinity than IL-13Rα1; the IL-13Rα2 receptor is considered a decoy receptor because it lacks a cytoplasmic signaling tail. However, the cytoplasmic domain of IL-13Rα2 may attenuate IL-4 signaling by inhibiting dimerization with γc or IL-13Rα1. (C) When IL-4 or IL-13 binds to a type II receptor, JAK1 and JAK2/TYK2 are activated.

of pruritus in BP may include multiple mediators, such as cytokines, chemokines, proteases, and associated receptors [56]. The study by Hashimoto et al. indicated that eosinophil is related to pruritus severity of BP [56], presumably because of chemokines activated by eosinophils. A meta-analysis revealed that numerous chemokines were elevated in BP. The levels of CCL11 (eotaxin 1), CCL17, and tumor necrosis factor-α were elevated in blister fluid, whereas CCL26 (eotaxin 3) was elevated in serum [57]. CCL11 and CCL26 are important chemokines that mediate eosinophil infiltration and degranulation. Additionally, IL-31, a Th2 cytokine primarily expressed by eosinophils in BP [58], may also contribute to pruritus in BP.

Because IgE and eosinophils are mostly associated with the Th2 immune response, further investigations are needed to determine whether BP fits in the category of Th2-dominant disease. The cytokine patterns of Th1-dominant and Th2-dominant immune diseases are distinct. Most autoimmune diseases regarded as Th1-associated conditions exhibit high levels of IL-2, interferon-γ, and IL-12. Th2-associated diseases, such as allergic and atopic dermatitis, are characterized by high levels of IL-4, IL-5, and IL-13. By detecting the cytokine levels in BP, researchers identified greater numbers of IL-4/13-producing cells at the lesion site or perilesional site of BP [59,60], indicating an unneglectable involvement of Th2-mediated autoimmunity in BP pathogenesis.

Roles of IL-4 and IL-13 in BP

Sources of IL-4 and IL-13

Th2 cells are presumed to have key roles in the pathogenesis of allergic disorders, such as AD, asthma, and chronic rhinosinusitis. As described above, BP is regarded as a Th2-related immune response disease that involves overexpression of IL-4, IL-5, and IL-13 in the past decades, however, the discoveries of cells other than Th2 cells that produce IL-4 and IL-13 add to its complexity. It was revealed that group 2 innate lymphoid cells (ILC2s) are important sources of IL-13, while follicular helper T cells (Tfh) are sources of IL-4 [61,62].

ILC2 cells are innate lymphoid cells that can produce large amounts of type 2 cytokines. Considerable research has been conducted regarding the role of

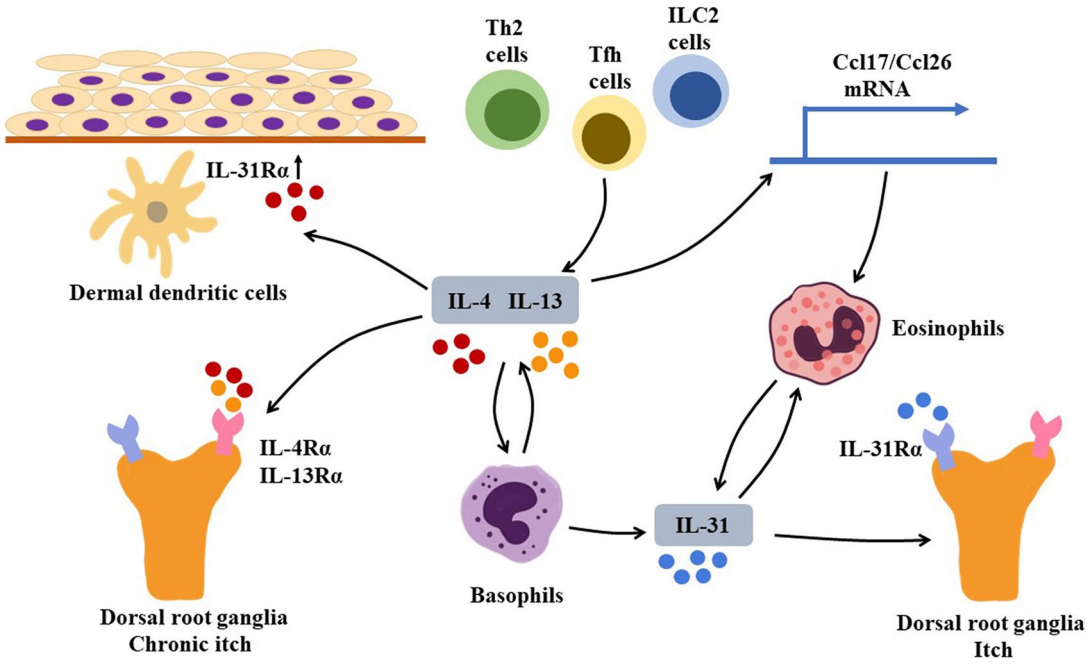

Figure 2. Mechanism of pruritus in BP Sources of IL-4 and IL-13 may include T helper 2 (Th2) cells, group 2 innate lymphoid cells (ILC2s), and follicular helper T (Tfh) cells. IL-4 and IL-13 can activate basophils that produce IL-31, a cytokine that induces pruritus by stimulating IL-31Rα on sensory neurons. Additionally, basophils can produce IL-4 and IL-13; IL-31 can recruit eosinophils to lesion sites, contributing to the formation of a positive feedback loop that exacerbates pruritis. In addition to IL-31, IL-4, and IL-13 can directly cause chronic pruritus by interacting with IL-4Rα and IL-13Rα on sensory neurons. Furthermore, IL-4 can induce upregulation of IL-31Rα on dermal dendritic cells. The augmented IL-31/IL-31Rα interaction can lead to increased production of CCL17 and CCL22, thus promoting Th2-related immune response.

ILC2s in asthma. In mouse studies regarding the pathogenesis of asthma, it was revealed that ILC2s are major sources of IL-5 and IL-13 [63]. Interestingly, the authors found that when patients with asthma were treated with corticosteroids, cytokines produced by Th2 cells decreased but cytokines of ILC2s were not suppressed. These findings may explain the corticosteroid resistance in asthma patients [63]. The study from Bartemes et al. revealed that ILC2s were abundant in the peripheral blood of patients with allergic asthma, and ILC2s could be recruited to mucosal tissues through peripheral blood circulation. Furthermore, ILC2s also have the ability to induce eosinophil acumination in tissue [64]. However, allergic rhinitis, another Th2-dominant immune response disease, did not show an increase in ILC2s [64]. In skin diseases, ILC2s have been proven to be involved in AD [65], but there has been no research concerning ILC2s in BP. Although ILC2s may not able to be markers for Th2 immune response, further studies are needed to fully elucidate their role.

Tfh cells are a subset of $CD4^+$ helper T cells, with distinct but overlapping molecular mechanisms as Th2 cells to regulate IL-4 [66]. King et al. identified Tfh responses in the context of Th2 immunity, suggesting that Tfh cells might be the main source of IL-4 *in vivo* [67]. It was also reported that IgE and IgG1 antibody responses in allergic disease were mainly controlled by IL-4-secreting Tfh cells, rather than Th2 cells [61]. In the study of autoimmune bullous disease, it was revealed that Tfh-like $CD4^+$ tissue-resident memory cells were present in pemphigus lesions [68]. In BP, Li et al. found that Tfh cell counts were significantly higher in the peripheral blood of patients with BP and they observed an obvious decrease in Tfh levels after effective therapy. This indicates that Tfh cells are involved in the pathogenesis of BP [69]. However, to our knowledge, no research has been conducted regarding the presence and involvement of Tfh-like cells in the skin of patients with BP.

Signaling of IL-4 and IL-13

IL-4 can bind to two receptors, the type I receptor and type II receptor. Type I receptors are mainly distributed on lymphocytes and myeloid cells, whereas type II receptors are present on myeloid cells and all non-hematopoietic cells (Figure 1) [70]. Type I receptors are composed of IL-4Rα and γc, whereas type II receptors are composed of IL-4Rα and IL-13Rα1 [71].

IL-13Rα1 not only serves as a subunit of type II receptors for binding IL-4 but also a receptor for IL-13 (Figure 1). Once IL-4 binds with type I receptors or type II receptors, downstream signaling molecules, such as Janus kinase (JAK) 3, JAK1, or JAK2/tyrosine kinase 2 (TYK2) are activated [71]. These signaling molecules then phosphorylate with each other to induce changes in the cytoplasmic tails of receptors, which serve as docking sites for downstream signaling molecules like signal transducer and activator of transcription 6 (STAT) and insulin receptor substrate (IRS) [71]. STAT6 and IRS are the two main pathways in IL-4/13 signaling. STAT6 can bind with DNA sequences to initiate gene transcription, while the IRS-2 pathway does not translocate to the nucleus but activate signaling molecules like PI3-K [72,73] to initiate gene transcription. The STAT6 pathway has been well-studied in asthma, where it is responsible for Th2 differentiation and eosinophil migration. However, the IRS pathway is presumed to be critical for cancer proliferation and metastasis [71].

Similar to IL-4, IL-13 can activate STAT6 by combining the type II receptor [71]. When IL-13 combines with the type II receptors, the following signaling pathway is similar to IL-4 signaling. JAK1 or JAK2/TYK2 will be activated and gene transcription will be conducted by the STAT6 pathway. In addition to the IL-13Rα1 in type II receptors, IL-13Rα2 is an alternative receptor chain for IL-13 that exhibits higher binding affinity [71]. When combined with IL-13, IL-13Rα2 does not initiate the typical STAT6/IRS signaling to promote IL-4-driven inflammation. Therefore, IL-13Rα2 used to be considered merely a decoy receptor of IL-13 for the lacking of cytoplasmic tail signaling motifs. However, there has been increasing evidence that IL-13Rα2 has additional functions [74–76]. Andrews et al. reported that IL-13Rα2 can attenuate IL-4 signaling by interacting with the cytoplasmic tail of IL-4α [75].

Relationship between IL-4/13 and BP

IL-4 plays an important role in the differentiation of naive CD^{4+} T cells into Th2, forming a positive feedback loop between Th2 cells and IL-4 [77,78]. By suppressing pro-inflammatory cytokines like IL-1, IL-6, IL-8, interferon-γ, and tumor necrosis factor-α, IL-4 can also hinder the differentiation of naive CD^{4+} cells into Th1 cells [79]. Therefore, IL-4 can enhance the Th2 response and inhibit the Th1 response to induce Th2 polarization. As a B cell helper, the enhanced Th2 immune response promotes the production of autoantibodies, such as autoimmune IgG and IgE, leading to tissue damage in BP. In addition to promoting IgE production by regulating Th2 differentiation, IL-4 is an essential factor for class switching to IgG1 and IgE in B cells. IL-13 is also able to induce class switching, however with less ability compared to IL-4 [80]. As noted above, IgG1 and IgE autoantibodies are key factors in the development of BP.

The underlying pathogenesis of pruritis in BP is complicated, where both IL-4 and IL-13 play important roles (Figure 2). IL-4 and IL-13 are known to activate mast cells, basophils, and macrophages [80]. Among these cells, basophils can produce IL-31, a cytokine that stimulates IL-31Rα on sensory neurons and induces cutaneous nerve growth and branching, leading to severe pruritus [81–84]. High levels of IL-31 have been detected in the serum and blister fluid of patients with BP [85]. There are studies suggesting that basophils secreted IL-31 could recruit eosinophils to the site of the lesions [86]. As the recruited eosinophils produce IL-4 and IL-13, more basophils are activated to produce IL-31, thus forming a positive feedback loop to promote pruritus in BP. Furthermore, basophils can produce IL-4 and IL-13 [65,87]. In addition to its effects on the levels of IL-31, IL-4 can interfere with the expression of IL-31Rα. In one study, IL-4 was found to stimulate the expression of IL-31Rα in mouse bone marrow-derived dermal dendritic cells in a dose-dependent manner [82]. Increased interactions between IL-31 and IL-31Rα led to greater production of chemokines that promote Th2 cell response, resulting in the exacerbation of pruritis symptoms [82]. Apart from IL-31, IL-4/13 can directly induce pruritis. Oetjen et al. observed that IL-4Rα and IL-13Rα were expressed on mouse dorsal root ganglia (neurons that mediate skin sensation), revealing that IL-4 and IL-13 can act directly on sensory neurons and might promote chronic itch through the JAK/STAT signaling pathway discussed above [88]. However, Hashimoto et al. indicated that IL-13, rather than IL-4, was correlated with pruritus severity in BP [56]. They speculated that in addition to interacting with IL-13R, IL-13 may contribute to pruritis symptoms by recruiting eosinophils to sites of inflammation in BP lesions.

The distribution pattern and disease correlation of IL-4/13 with BP were also studied. The study by Teraki et al. showed that BP was a unique organ-specific autoimmune disease with increasing numbers of skin-homing IL-4- and IL-13-producing cells [59]. In their study, treatment with corticosteroids led to a significant reduction in the number of IL-13-producing cells, along with an improvement in clinical symptoms. The

distribution of these IL-4/13 producing cells may be different since it was also reported that IL-4 was mostly localized within the superficial dermis while IL-13 was localized both in the upper and deep dermis [60]. The mechanisms underlying these cytokine distribution patterns require further exploration; the patterns highlight the complexity of local immunological pathogenesis in BP. It was also reported that IL-4 concentration was remarkably higher in blisters than in serum in patients, which indicates that IL-4 may be a major contributor to local skin lesion formation than IL-13 [89].

Considering the roles of IL-4 and IL-13 in amplifying Th2 polarization, autoantibody class switching, pruritus, and skin-homing T cells-cell accumulation, it is reasonable to target both cytokines in the treatment of BP.

Anti-IL-4/13 therapy as a potential treatment for BP

Th2-related diseases, including BP, often present with similar characteristics: elevated levels of IgE autoantibodies, higher numbers of circulating and infiltrating eosinophils, and increased production of downstream chemokines [90,91]. When considering the reduction of the overall Th2 response, it is reasonable to target the Th2 axis. Drugs targeting cytokines in the Th2 axis have already been used for AD treatment with satisfactory efficacy [11]. Due to the similarity of cytokine patterns between BP and AD, the anti-IL-4/13 treatment is promising in managing BP.

Dual targeting of IL-4/13: dupilumab

AD is immunologically regarded as a Th2-dominant immune response disease. IL-13 acts as a disease-inducing agent, whereas IL-4 acts as a Th2 response amplifier [10]. Dupilumab targets both IL-4 and IL-13 and therefore have a potential impact on the Th2 axis, such as interfering with positive feedback loops in the Th2 response, downregulating the concentration of IgE levels, and infiltration of eosinophils. Dupilumab has been reported to significantly downregulate serum levels of CCL17, a key regulator of the Th2 immune response [10]. In multiple clinical trials, dupilumab has demonstrated impressive efficacy in managing AD and showed satisfying tolerability in AD patients under 18 years old (Table S1). Considering the impressive efficacy of dupilumab, ongoing clinical trials are studying the use of dupilumab in other dermatoses, such as allergic contact dermatitis (NCT03935971), cholinergic urticaria (NCT03749148), and chronic hand eczema (NCT04512339).

Similar to AD, in patients with BP, dupilumab may play a major part in relieving itch by interrupting the neuronal stimulation caused by IL-4 and IL-13. In one multicenter case series, the use of dupilumab was investigated in 13 patients with BP [13] (Table 1). Some patients received concomitant medications, including systemic or topical corticosteroids and methotrexate. The study used the same dosing approved for AD: initially, 600 mg subcutaneously, followed by 300 mg subcutaneously every 2 weeks [13]. In that case series, 53.8% (7 of 13) patients achieved disease clearance, defined as the clearance of both bullae and pruritus. 76.9% (10 of 13) patients showed improvement of bullae with residual pruritus. Furthermore, no obvious adverse events were reported in patient records with dupilumab administration. In a recent systematic review, similar results were reported (Table 1). The complete remission rate in patients was 66.7% (24 of 36) within 4.5 months of dupilumab treatment; the recurrence rate was 5.6% (2 of 36) [28]. The usage of dupilumab has also been studied in a case-control paradigm, along with methylprednisolone and azathioprine, for the treatment of moderate-to-severe BP (Table 1). In that study, the group with additional dupilumab treatment demonstrated better performance, compared with the group receiving methylprednisolone and azathioprine. The dupilumab group exhibit a shorter time to blistering cessation and steroid tapering, whereas the difference in length of hospital stay was not statistically significant. Nevertheless, patients in the dupilumab group achieved more rapid pruritus relief within the first 2 weeks. Surprisingly, there was no difference in the time to the reduction of eosinophil count between the two groups. A possible explanation for this lack of difference is that methylprednisolone may be sufficiently effective to reduce eosinophil count within a few hours [14]. There is also an ongoing clinical trial (NCT04206553) that aims to assess the safety and tolerability of dupilumab administered to patients with BP, and to evaluate its effect on pruritus. This may provide additional evidence for the use of dupilumab in BP, but further clinical trials are needed.

Antibodies targeting IL-13

Tralokinumab is a humanized monoclonal IgG4 antibody that inhibits the binding of IL-13 to IL-13Rα1 and IL-13Rα2. The binding of tralokinumab to IL-13Rα1 interferes with the heterodimerization of IL-13Rα1 with IL-4Rα, whereas the binding of tralokinumab to IL-13Rα2 inhibits

endogenous regulation. In a series of clinical trials (ECZTRA 1–6), tralokinumab demonstrated satisfactory efficacy and safety in the treatment of AD (Table S1). In 52-week phase 3 trials (NCT03131648 and NCT03160885), participants treated with tralokinumab demonstrated improvements in primary endpoints and all key secondary endpoints, compared with participants given placebo. The clinical trials also showed that most tralokinumab responders at week 16 continued to exhibit good tolerance at week 52 without rescue treatment [92]. In the safety assessment, most adverse events were non-serious; upper respiratory tract infection and conjunctivitis were the most common side effects.

Lebrikizumab is also an autoantibody drug that targets IL-13. A phase 2b study (NCT03443024) found that lebrikizumab provided rapid, dose-dependent efficacy with a favorable safety profile in adult AD patients [93]. In that study, the lebrikizumab group showed significant improvement in the primary endpoint at week 16, compared with the placebo group. In contrast to tralokinumab, lebrikizumab only inhibits the binding of IL-13 to IL-13Rα1; it cannot inhibit the binding of IL-13 to IL-13Rα2 [94]. Ideally, by analyzing the efficacy of tralokinumab and lebrikizumab, it may provide evidence of the different biological effects of IL-13Rα1 and IL-13Rα2 signaling. To our knowledge, no clinical trials have explored these effects thus far. However, Miyano et al. developed a mathematical model to study the efficacies of biological drugs based on a meta-analysis of the most recent clinical trials in AD [95]. According to their model, lebrikizumab was more effective than tralokinumab in the treatment of AD. Furthermore, the effectiveness of tralokinumab was 44% of the lebrikizumab effectiveness in terms of inhibiting IL-13 signaling, which may be explained by the finding that IL-13Rα2 mainly acts as a decoy receptor for IL-13 and may inhibit the IL-4 signaling cascade. They also reported that dupilumab and lebrikizumab showed comparable efficacy, suggesting that IL-13 is the main contributor to the efficacy of dupilumab in AD because lebrikizumab does not target IL-4. Therefore, we expect that IL-13 antibodies will find applications in the treatment of BP.

Possible side effects of anti-IL-4/13 therapies

Although anti-IL-4/13 therapy sounds promising, it may have various side effects. The target receptors are not exclusive to hematopoietic cells. They are also distributed in myeloid cells and all non-hematopoietic cells [70]. The side effects of anti-IL-4/13 therapy may be complex because of the wide receptor distribution. Because of similarities in the pathological mechanisms of BP and AD, the potential side effects of BP can be explored by reviewing relevant studies of AD.

Notably, IL-4/13 signaling has been shown to participate in metabolism, tissue regeneration, remodeling, cancer, as well as cognitive function [96]. IL-4 deficient mice and IL-13 deficient mice both showed severe cognitive impairment, as measured by the Morris water maze test [97,98]. The authors suggested that by stimulating astrocytes in the meninges and hippocampus, Th2 cytokines may improve cognitive functions [97]. There is a consensus that BP is closely associated with neurodegenerative diseases, and that patients with BP are more likely to develop cognitive impairment [99–101]. To our knowledge, there is no consensus regarding the levels of IL-4 and IL-13 in the cerebrospinal fluid of patients with BP, or whether IL-4 and IL-13 contribute to cognitive impairment in BP. In healthy conditions, the blood-brain barrier restricts the access of macromolecules (e.g. anti-IL-4/13 drugs) to the central nervous system. However, in patients with neurodegenerative diseases, disruption of the blood-brain barrier is common [102]. It is unclear whether anti-IL-4/13 drugs can cross the blood-brain barrier in certain pathological conditions. Because there is no consensus regarding the mechanisms that underlie the concurrent onset of BP and neurodegenerative diseases, further studies are needed to determine whether anti-IL-4/13 therapy will increase susceptibility to cognitive damage or dementia among patients with BP.

A systematic review was performed concerning the side effects of anti-IL-4/13 therapy in preclinical and clinical studies from 2006 to 2016. It found no significant increases in major side effects, such as severe infections, malignancies, or cardiovascular events. Furthermore, compared with IL-4/13 dual targeting therapies, biologics targeting IL-13 alone did not exhibit differences in terms of safety [103]. Overall, anti-IL-4/13 therapy is presumed to be safe for most patients.

Conclusion

As typical Th2 cytokines, IL-4 and IL-13 may contribute to the pathogenesis of BP in multiple ways. The possible mechanisms include: promoting Th2 cell polarization, driving immunoglobulin class switching to IgG1 and IgE, interfering with IgG isotype switching by promoting the production of IgG4, recruiting eosinophils and basophils, and mediating pruritus by increasing the production of IL-31. The management

of BP is challenging due to the side effects of traditional therapies including corticosteroids and immunosuppressants, whereas IL-4/13 antagonists, such as dupilumab had demonstrated satisfactory outcomes in preliminary BP clinical studies. Thus, IL-4/13 monoclonal antibodies in BP deserve further study and might be regularly used for BP therapy in the future.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author contributions

Fangyuan Chen and Li Li contributed to the conceptualization of the review. Fangyuan Chen and Yiman Wang wrote the manuscript. Xinyi Chen constructed the figures. Fangyuan Chen and Nan Yang conducted the literature search and constructed the tables.

Disclosure statement

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