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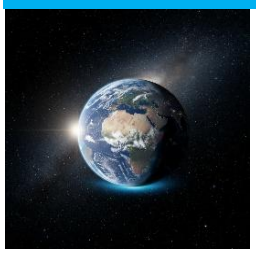

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# The role of Dupilumab in the treatment of Bullous Pemphigoid, Pemphigus and Hailey-Hailey Disease: A Narrative Review

Natalia Będkowska-Kuśmierek, ORCID https://orcid.org/0009-0003-6385-1427

nbedkowskakusmierek@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Sabina Zaborowska, ORCID https://orcid.org/0009-0004-4742-5046

sab.zaborowska@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Paulina Pawlak, ORCID https://orcid.org/0009-0000-6102-1727

paulinaa379@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Olaf Wojcieszuk, ORCID https://orcid.org/0009-0000-7006-3494

olaf@wojcieszuk.pl

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Łukasz Starczewski, ORCID https://orcid.org/0009-0000-2258-4885

lukasz.starczewski7@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Adrianna Babik, ORCID https://orcid.org/0009-0001-2421-499X

adababik4@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Kamila Kamińska, ORCID https://orcid.org/0009-0008-1721-4431

kaminska.k4m@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Matylda Będkowska-Kuśmierek, ORCID https://orcid.org/0009-0004-2707-2167

matylda.bedkowskak@o2.pl

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Anna Złotnik, ORCID https://orcid.org/0009-0000-9011-7488

annazlotnik01@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Kinga Krzysztofik, ORCID https://orcid.org/0009-0004-0184-8940

kingakrzysztofik7@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

**Corresponding Author**

Natalia Będkowska-Kuśmierek, nbedkowskakusmierek@gmail.com

## Abstract

**Background:** Autoimmune bullous diseases (AIBDs) and Hailey-Hailey disease are chronic skin disorders characterized by blister formation, pruritus, and reduced quality of life. Standard treatments, including systemic corticosteroids and immunosuppressants, often cause adverse effects and may not achieve long-term remission. Dupilumab, a monoclonal antibody targeting IL-4 and IL-13, has emerged as a promising alternative.

**Aim:** To evaluate the efficacy and safety of dupilumab in patients with bullous pemphigoid, pemphigus vulgaris and foliaceus, and Hailey-Hailey disease.

**Material and Methods:** Literature review including meta-analyses, randomized trials, retrospective studies, and case reports on dupilumab use in AIBDs and Hailey-Hailey disease. Disease activity was assessed using PDAI, BPDAI, or clinical evaluation; quality of life and adverse events were summarized.

**Results:** In bullous pemphigoid, dupilumab reduced disease activity, pruritus, and cumulative corticosteroid dose, with most patients achieving complete or partial remission. Evidence in pemphigus vulgaris and foliaceus is limited but suggests potential benefit, particularly in patients ineligible for rituximab. In Hailey-Hailey disease, dupilumab improved lesions and quality of life, although relapse after discontinuation was reported. Therapy was generally well tolerated- with main adverse events being: injection site reactions, conjunctivitis, and eosinophilia.

**Conclusions:** Dupilumab is an effective and safe option in bullous pemphigoid, offering pruritus relief and steroid-sparing benefits. Its use in pemphigus and Hailey-Hailey disease is promising but experimental. Further high-quality studies are needed to confirm long-term efficacy and safety.

**Keywords:** Dupilumab; Bullous pemphigoid; Pemphigus vulgaris; Pemphigus foliaceus; Hailey-Hailey disease; Autoimmune bullous diseases.

## 1.1 Introduction:

Autoimmune bullous diseases constitute a heterogeneous group of conditions characterized by the formation of intraepidermal blisters, in which fluid accumulates between the layers of the epidermis (e.g., pemphigus vulgaris, pemphigus foliaceus), or subepidermal blisters, in which fluid accumulates beneath the epidermis (e.g., bullous pemphigoid) [1]. They are most commonly associated with the production of specific autoantibodies directed against proteins that form intercellular junctions in the epidermis.

In pemphigus, IgG4-class antibodies are produced against desmogleins- structural proteins of desmosomes- which consequently leads to acantholysis. Desmosomes are intercellular junctions responsible for the adhesion of keratinocytes forming the layers of the epidermis [2].

In patients with bullous pemphigoid, specific IgG and IgE antibodies are produced against hemidesmosomal proteins with molecular weights of 180 kDa (BP180) and 230 kDa (BP230) [3]. Factors that provoke and exacerbate the pathogenesis of pemphigus and pemphigoid include viral infections, ultraviolet radiation, and pharmacotherapy (e.g., amoxicillin, captopril, furosemide, DPP-4 inhibitors such as gliptins, or PD-1 inhibitors) [4].

In addition to antibody-mediated bullous diseases, Hailey-Hailey disease is also recognized. This is a genodermatosis inherited in an autosomal dominant manner, in which acantholysis leads to the formation of intraepidermal blisters. The pathogenetic basis is a mutation in the ATP2C1 gene, leading to impaired calcium ion transport within epidermal cells, which directly results in the aforementioned acantholysis and the formation of painful blisters [5].

In pemphigus vulgaris, the majority of patients present with flaccid blisters and erosions localized on the mucous membranes (mainly the oral cavity) and on the skin, whereas in

pemphigus foliaceus, lesions are confined exclusively to the skin [6]. Blisters in bullous pemphigoid are tense and localized mainly on the trunk and in the flexural areas of the limbs. They are very often accompanied by intense pruritus, which significantly impairs patients' quality of life [1]. Individuals affected by Hailey-Hailey disease experience recurrent episodes of flaccid blisters in intertriginous areas (armpits, groin, inframammary, and perianal regions) accompanied by intense pruritus.

Due to burdensome pruritus, constant skin damage, and pain, patients suffering from the aforementioned diseases experience a significant deterioration in quality of life, including sleep disturbances, chronic fatigue, and limitations in physical activity. This group of patients also very frequently exhibits marked reduction in self-esteem as well as depressive or anxiety episodes. A key element of care is the standardized assessment of disease severity. In pemphigus, the most commonly used and best-validated scale is the Pemphigus Disease Area Index (PDAI), enabling a detailed assessment of lesions on smooth skin, the scalp, and mucous membranes. In bullous pemphigoid, the Bullous Pemphigoid Disease Area Index (BPDAI) is applied, which additionally accounts for the severity of pruritus- one of the dominant symptoms of this condition. In Hailey-Hailey disease, no uniform, universally accepted assessment scale exists. In clinical practice, various modifications based on the extent of lesions, the presence of erosions, and subjective symptoms (pain and pruritus) are used, often supplemented by the DLQI quality of life index. Due to the severe, chronic course of these conditions and their negative impact on mental health, early diagnosis and implementation of targeted treatment are of key importance.

Treatment of pemphigus is based on classifying the patient according to disease severity (most commonly using the PDAI scale) and frequency of relapses. Patients with mild pemphigus (PDAI < 15) are treated with oral prednisone/prednisolone at a dose of 0.5–1.0 mg/kg/day. Additionally, therapy may be supplemented with azathioprine, mycophenolate mofetil, or mycophenolic acid. Patients with moderate or severe disease (PDAI > 15) receive a course of rituximab (2 × 1 g, 14 days apart) along with oral prednisone/prednisolone therapy (0.5–1.0 mg/kg/day). Azathioprine, mycophenolate mofetil, or mycophenolic acid may also be used as adjunctive therapy at the above-mentioned doses. In patients who have not achieved remission, a repeat course of rituximab is permitted while continuing steroid therapy and immunosuppressive agents. Immunoadsorption or intravenous immunoglobulins (IVIG) at a

dose of 2 g/kg/month may serve as alternatives [7]. It is important to note that pemphigus treatment is chronic in nature and lasts from several months to several years. This involves patients receiving high doses of glucocorticosteroids, which frequently generates adverse effects such as weight gain, mood fluctuations, arterial hypertension, and worsening glycemic control. Additionally, some patients have contraindications to rituximab therapy, which is nonetheless considered a safe first-line treatment in moderate and severe pemphigus as well as in relapsing cases [8].

Treatment of mild bullous pemphigoid (BPDAI < 20) is based on topical therapy with very high-potency glucocorticosteroids (e.g., clobetasol propionate 0.05%) in combination with possible oral steroid therapy (prednisone/prednisolone). It should be emphasized that patients with bullous pemphigoid, due to their often advanced age, are particularly susceptible to complications of chronic systemic steroid therapy. For this reason, oral steroids are recommended primarily in more severe forms. In moderate or severe cases (BPDAI > 20), in addition to topical treatment, immunosuppressive or anti-inflammatory agents are used, such as doxycycline, methotrexate, mycophenolate mofetil, or azathioprine. In relapses of bullous pemphigoid, rituximab, immunoadsorption, or IVIG are used [7].

In Hailey-Hailey disease, the main therapeutic goals focus on controlling flares, improving quality of life, and extending the duration of remission. Topically- similar to pemphigoid- very high-potency glucocorticosteroids are used. Due to frequent bacterial and fungal superinfections of skin lesions, patients are treated with antifungal agents and antibiotics (both topically and systemically). Oral treatment primarily involves glucocorticosteroids, but also tacrolimus or cyclosporine A, which act on cytokines IL-6 and IL-8, playing a key role in regulating the expression of the ATP2C1 gene. Eliminating triggering factors must not be overlooked: high temperatures, sun exposure, sweating, and excessive stress. Patients are advised to wear loose clothing to avoid friction in intertriginous areas and to limit physical activity that exacerbates this process [9].

Despite the availability of the above standard methods, the treatment of these conditions still represents a significant clinical challenge. This is due to the adverse effect profiles of the drugs, frequent relapses, and reduced quality of life in patients. Consequently, new, more targeted and effective treatment methods are being actively sought. One potential therapeutic alternative is

the use of biological agents with a more precise mechanism of action compared to rituximab. Rituximab, by acting on the CD20 molecule on the surface of B lymphocytes, causes their destruction, resulting in profound immunosuppression and the risk of serious infections in patients. Dupilumab is a modern biological agent that plays an immunomodulatory role.

Dupilumab is a fully human monoclonal antibody directed against the alpha subunit of the receptor for interleukin-4 (IL-4Rα), shared by IL-4 and IL-13 [10]. This allows the drug to block signaling pathways mediated by both cytokines. Interleukin-4 (produced by Th2 lymphocytes) participates in the differentiation of Th0 lymphocytes toward Th2, acting through a positive feedback mechanism. Furthermore, it induces B lymphocyte proliferation and stimulates class switching of antibodies toward IgG4 and IgE. Interleukin-13 also stimulates B lymphocyte proliferation and- similarly to IL-4- participates in class switching of antibodies to IgE. Both cytokines play a key role in the pathomechanism of type 2 inflammation [11]. For this reason, dupilumab has found application in the treatment of diseases with dominant type 2 inflammation. In dermatology, it has been successfully used for many years in the treatment of atopic dermatitis in adults and children over 6 months of age [12]. Outside of dermatology, the drug is used in the treatment of asthma, chronic sinusitis with nasal polyps, and eosinophilic esophagitis [11].

### 1.2.1. Research Objective:

The main aim of this study is to evaluate the efficacy and safety profile of dupilumab use in patients with bullous pemphigoid, pemphigus vulgaris and foliaceus, and Hailey-Hailey disease.

### 1.2.2. Research Problems:

1. What is the pathophysiological rationale for the use of dupilumab in the treatment of bullous diseases, in particular pemphigus, bullous pemphigoid, and Hailey-Hailey disease?

2. Does the use of dupilumab enable a significant reduction in the cumulative dose of systemic glucocorticosteroids (the so-called steroid-sparing effect) in patients with bullous diseases?
3. What is the safety profile of dupilumab and the incidence of adverse effects in patients with bullous diseases?

## 2. Research Materials and Methods:

A narrative review of the literature was conducted using the Pubmed/MEDLINE, Google Scholar databases. The search strategy was designed to identify publications evaluating the efficacy, safety, and potential mechanisms of action of dupilumab in autoimmune blistering diseases and Hailey-Hailey disease. The following combinations of keywords were used: “dupilumab AND bullous pemphigoid”, “dupilumab AND pemphigus”, “dupilumab AND Hailey-Hailey disease”, “dupilumab AND blistering diseases”, as well as “IL-4 AND IL-13 AND bullous diseases”.

Articles published between January 2015 and March 2026 were considered. Additionally, selected earlier publications were included when essential for understanding the pathogenesis of autoimmune bullous diseases and the immunological basis of targeted therapies. Only peer-reviewed original research articles and review papers published in English were included.

Studies conducted in human populations were prioritized, including randomized controlled trials, observational studies, systematic reviews, and meta-analyses. Due to the limited availability of large-scale studies, case reports and case series were also included, particularly for pemphigus and Hailey-Hailey disease. Selected experimental and translational studies were considered when relevant to the understanding of immunological mechanisms, including the role of interleukin 4 and interleukin 13 in type 2 inflammation.

Titles and abstracts were screened to assess relevance. Full-text articles were evaluated for eligibility. Publications not related to dupilumab therapy or not addressing blistering diseases were excluded. Studies focusing exclusively on unrelated dermatological conditions or lacking clinical relevance were also excluded. Conference abstracts, editorials, and non-peer-reviewed publications were not included.

After screening and eligibility assessment, a total of 28 sources met the inclusion criteria and were included in the final qualitative synthesis, consisting of 27 peer-reviewed articles and 1 authoritative book chapter providing essential clinical background

### 3.1. Dupilumab in the Treatment of Bullous Pemphigoid

In bullous pemphigoid, the inflammatory process dominated by Th2 lymphocytes plays a key role in the pathomechanism of blister formation, eosinophilia, and pruritus. Elevated concentrations of interleukin-4 and -13 are observed in patients in peripheral blood, serum, and in blister fluid collected directly from blisters. Furthermore, the main autoantibodies generated against the BP180 and BP230 proteins of the basement membrane are IgE and IgG class antibodies, produced by B lymphocytes [13]. For this reason, the use of dupilumab may represent a promising alternative to standard treatment of bullous pemphigoid.

In a single-arm meta-analysis published in February 2026 by Chen et al., data from 24 studies (23 retrospective studies, 1 case report) involving a total of 587 patients with bullous pemphigoid were analyzed. The results of the meta-analysis showed that the rate of complete resolution of lesions in patients treated with dupilumab (in combination with other systemic therapy or without it) was 68%. The rate of complete resolution of lesions in patients treated with dupilumab alone was estimated at 63% [14].

Thapa et al. analyzed data from 6 studies (3 retrospective cohort studies and 3 case series) involving a total of 207 patients with bullous pemphigoid. The results of the meta-analysis showed that the rate of complete resolution of lesions in patients treated with dupilumab was 54.8%. The combined response rate (including both complete and partial response) was 86.5%. In parallel, the authors conducted an umbrella review in which they identified 8 systematic reviews (including 3 containing meta-analyses) published between 2022 and 2025. However, it was found that the majority of these publications were characterized by critically low methodological quality according to the AMSTAR2 scale and a very high degree of overlap of the same source data [15].

Opolski Nunes da Silva et al., in their 2025 meta-analysis, evaluated data from four studies involving a total of 127 patients with bullous pemphigoid (53 patients treated with dupilumab

in combination with glucocorticosteroids and 74 patients in the control group receiving standard steroid therapy alone). The median age of patients was 74 years in the study group and 69 years in the control group, respectively. The results of the meta-analysis showed that the addition of dupilumab to standard therapy significantly shortened the time to complete cessation of new blister formation (mean difference [MD] = −5.13 days; 95% CI: −7.12 to −3.15; $p < 0.0001$). Furthermore, a greater reduction in the BPDAI disease severity index was observed in the dupilumab-treated group (MD = −3.90; 95% CI: −5.52 to −2.27; $p < 0.0001$), as well as a significant decrease in pruritus severity assessed on the NRS scale (standardized mean difference [SMD] = −1.37; 95% CI: −2.02 to −0.72; $p < 0.0001$) compared to baseline values. The analysis also demonstrated a significant steroid-sparing effect. The time required to reduce the methylprednisolone dose was shorter by an average of 25.78 days (95% CI: −36.42 to −15.13; $p < 0.0001$), and the total cumulative dose of the drug was lower by an average of 533.88 mg (95% CI: −784.45 to −283.31; $p < 0.0001$) in the dupilumab group. No statistically significant differences were found regarding the maintenance dose of glucocorticosteroids ($p = 0.14$) [16].

In a phase II/III randomized clinical trial (RCT), the efficacy and safety of dupilumab were evaluated in 106 patients with bullous pemphigoid (NCT04206553). The study included patients aged 18–90 years with moderate or severe disease (BPDAI ≥ 24), intense pruritus (≥ 24 points on the NRS scale), and general performance ≥ 50 on the Karnofsky scale. Patients received subcutaneous dupilumab at a dose of 300 mg or placebo every 2 weeks for 52 weeks, in combination with prednisone/prednisolone at a dose of 0.5 mg/kg/day. After 6 weeks of treatment, the glucocorticosteroid dose was gradually reduced over the following 16 weeks. The primary endpoint, defined as sustained remission at week 36 (i.e., achieving complete remission without glucocorticosteroids by week 16, no relapse, and no need for rescue therapy by week 36), was achieved in 5 patients (20%) in the dupilumab group compared to 1 patient (4%) in the placebo group ($p = 0.0114$). All key secondary endpoints at week 36 were also met in favor of dupilumab, including:

≥ 90% reduction in disease severity ($p = 0.0003$),
Clinically meaningful reduction in pruritus ($p = 0.0006$),
Overall reduction in disease activity ($p = 0.0021$),
Greater number of days in complete remission without glucocorticosteroids ($p = 0.0072$).

The Liberty BP-ADEPT study confirmed greater efficacy and reduction in disease activity with dupilumab combined with glucocorticosteroids compared to the group receiving placebo and glucocorticosteroids in the treatment of moderate and severe bullous pemphigoid. Regarding quality of life, dupilumab proved to reduce the severity of pruritus in patients more quickly than standard therapy, which directly improved their quality of life. Based on the above data, dupilumab was approved by the Food and Drug Administration (FDA) in June 2025 for the treatment of moderate and severe bullous pemphigoid (approval by the European Medicines Agency is currently in progress) [17].

The most common adverse effects reported in patients during dupilumab therapy included: injection site reactions, conjunctivitis, eosinophilia, and herpes virus activation [14, 17].

In summary, dupilumab demonstrates efficacy in the treatment of bullous pemphigoid, particularly in reducing pruritus and disease activity, representing a possible therapeutic alternative. Additionally, it enables a reduction in the total cumulative dose of glucocorticosteroids, which in elderly patients reduces the risk of systemic complications and exacerbations of comorbidities induced by steroid therapy [16, 18]. However, further studies are needed to precisely confirm its long-term efficacy and safety.

### 3.2. Dupilumab in the Treatment of Pemphigus Vulgaris and Foliaceus

In terms of the potential pathomechanism of pemphigus vulgaris and foliaceus, excessive activity of Th17 lymphocytes along with the IL-17 they produce is described, as well as Th1 and Th2 lymphocytes generating IL-4 and IL-13. Some patients also exhibit eosinophilia in peripheral blood [6, 19]. In view of the above, dupilumab, as a drug that indirectly blocks the Th2 lymphocyte-dependent response, may represent a therapeutic alternative in selected cases of pemphigus vulgaris and foliaceus.

Rico et al. in 2025 described two cases of dupilumab use in patients with pemphigus vulgaris and one case with pemphigus foliaceus. In the first case, in a patient with pemphigus vulgaris, it was decided to forgo rituximab treatment due to a co-existing bladder cancer. The second patient, despite the use of prednisone and two rituximab infusions, did not achieve remission of oral mucosal lesions. This led to the introduction of dupilumab at an initiating dose of 600 mg,

followed by 300 mg every two weeks. Both patients achieved complete remission of symptoms. In the case of the patient with pemphigus foliaceus, rituximab was initially withheld due to a positive HBV DNA history. Despite 6 months of dupilumab therapy, this patient did not achieve remission, which, after a medical consultation, resulted in the discontinuation of dupilumab and the initiation of rituximab [20].

Edwards et al. in 2025 described the case of a 40-year-old man with pemphigus foliaceus who, despite complex treatment with intravenous immunoglobulins, methylprednisolone, and mycophenolate mofetil, did not achieve improvement in pruritus severity (NRS 10/10) or skin lesions. This led to the rescue use of dupilumab at an initiating dose of 600 mg and 300 mg every 2 weeks. After one year of dupilumab therapy, the skin lesions achieved complete remission and pruritus on the NRS scale dropped to 0/10 [21].

An important contraindication to the use of rituximab in pemphigus treatment is active tuberculosis. Mycobacterial infection necessitates modification of the therapeutic regimen. Such a case of pemphigus vulgaris in a patient with pulmonary tuberculosis was described by Chen et al. In a 35-year-old patient, due to the detection of active infection foci, primary immunosuppressive treatment of pemphigus was withheld and anti-mycobacterial therapy was initiated. After 2 months, the patient was admitted to the dermatology ward due to a rapid exacerbation of skin and mucosal lesions. He then received methylprednisolone, however without therapeutic effect. It was decided to add dupilumab. After 1.5 months of combined therapy, the PDAI index dropped from 97 to 42 points, and a decrease in peripheral eosinophilia and IgE antibody levels was also observed [22].

There are also scientific publications in the literature concerning the use of dupilumab in the treatment of pemphigus in pediatric patients (under 18 years of age).

Yun et al. in their 2025 paper presented the case of a 3-year-old boy diagnosed with childhood pemphigus vulgaris. The patient developed painful blisters and erosions in the oral cavity. Additionally, based on histopathological examination of esophageal biopsies, pemphigus vulgaris with co-existing eosinophilic esophagitis was diagnosed. The patient also had peripheral blood eosinophilia of 1.00–1.50 × $10^9$/L (normal: < 0.5 × $10^9$/L) and a marked increase in serum IgE concentration to 2460 IU/mL (normal: < 150 IU/mL). Prednisolone and dapsone had been used previously, but due to lack of improvement, dapsone was discontinued

and mycophenolate mofetil was added. This induced the development of proximal onychomadesis (separation of the nail plate from the matrix) and new skin blisters in the patient, accompanied by an increase in anti-DSG1 IgG and anti-DSG3 IgG antibody titers. Rituximab therapy was not pursued due to the ongoing COVID-19 pandemic and the family's concerns about profound immunosuppression. Taking into account the drug's successes in atopic dermatitis (type 2 inflammation), data from eosinophilic esophagitis studies, and reports in adults, dupilumab was initiated. At age 5, the patient received a loading dose of 175 mg (12 mg/kg), followed by a maintenance dose of 6 mg/kg every 2 weeks. Within 4 months of starting dupilumab, the skin, nail, and mucosal lesions improved significantly, and the desmoglein antibody titers decreased. The patient continued therapy at a dose of 200 mg every 2 weeks for 44 months. IgE levels also normalized, although the eosinophil count remained elevated (0.74 to 2.31 × $10^9$/L) and is subject to ongoing monitoring [23].

Maruschak-Love et al. in a case report published in 2026 presented the profile of a 16-year-old boy with diagnosed pemphigus vulgaris, in whom the disease developed following an upper respiratory tract infection. Initial treatment with prednisone (0.75 mg/kg/day) did not halt the progression of bullous lesions, which involved the face, genitals, and mucous membranes. Due to an unsatisfactory response to steroid monotherapy, dupilumab was added (initially 600 mg, then 300 mg every 2 weeks) as a steroid-sparing agent. Importantly, in this clinical case, the patient did not present features of atopy, had a normal IgE level, and a normal eosinophil count. The application of 10 months of dupilumab therapy allowed for rapid reduction of the prednisone dose to physiological levels and achievement of sustained disease quiescence (maintained for another 3 months after dupilumab discontinuation). The only adverse effects noted were complications of steroid therapy (weight gain and stretch marks), while no symptoms attributable to dupilumab itself were recorded [24].

In summary, the presented literature reports indicate that dupilumab may represent a potential therapeutic alternative for patients with pemphigus vulgaris and foliaceus. Although this drug blocks the Th2-dependent inflammatory pathway, it proves effective not only in individuals with features of atopy (high IgE or eosinophilia) [24], but also in patients without such immunological abnormalities. The particular value of dupilumab therapy is its high safety profile. It allows avoidance of rituximab-associated immunosuppression in high-risk groups (active infections such as tuberculosis, or malignancies) [20, 22] and facilitates the reduction

of glucocorticosteroid doses in children and adolescents, protecting them from systemic complications [23, 24]. However, it should be emphasized that current knowledge on this topic is based exclusively on case series reports. The literature still lacks multicenter randomized trials and meta-analyses that would definitively and unequivocally confirm the efficacy and safety profile of dupilumab in the treatment of pemphigus vulgaris and foliaceus.

### 3.3. Dupilumab in the Treatment of Hailey-Hailey Disease

Dupilumab, by blocking the signaling pathways mediated by IL-4 and IL-13, inhibits the inflammatory response mediated by Th2 cells. Although acantholytic dermatoses are traditionally considered primary disorders of keratinocyte adhesion, scientific evidence suggests that inflammatory pathways (in particular, the immune response involving Th2 lymphocytes) may exacerbate epidermal barrier dysfunction and directly contribute to the pathogenesis of these diseases. Alzahrani et al. suggested that inhibition of IL-4 and IL-13 may attenuate the effect of the chemokine ligand CCL26 on the CCR3 receptor. As a consequence, this may affect the mobilization of intracellular calcium and modify the disease process in Hailey-Hailey disease, which is based on a mutation in the ATP2C1 gene leading to impaired calcium ion transport within epidermal cells [5, 25].

In a systematic review published in 2025 by Liu et al., a case series was described involving a total of 11 patients (5 men and 6 women) with Hailey-Hailey disease (HHD) treated with dupilumab. All patients initially presented with painful erosions in intertriginous areas, typical of this condition. 91% of patients (10 out of 11) achieved significant clinical improvement, and in the majority, the response to treatment was durable over an observation period of 3 to 25 months. Importantly, discontinuation of therapy may lead to relapse (one such case was described). The therapy was well tolerated; the only more serious adverse effect was a case of de novo psoriasis in one patient, which required discontinuation of the biologic agent and initiation of topical steroid therapy [26].

Oillarburu et al. in a multicenter, retrospective cohort study of patients with Hailey-Hailey disease (HHD) treated with dupilumab, published in 2025, evaluated the effect of the drug after 6 months compared to baseline, using the IGA-C scale (Investigator's Global Assessment of

Change scale). Patients were classified as non-responders (IGA-C: 0 or +1) or responders (IGA-C: −1, −2, or −3), with a good response defined as a score of −2 or −3. Efficacy, understood as the percentage of responding patients, was analyzed with a 95% confidence interval (CI) using the Agresti-Coull method. Due to the limited sample size, statistical subgroup analyses were not performed. Additional objectives included evaluation of the safety profile, quality of life (QoL), need for analgesics and topical treatment, frequency of hospitalizations, and long-term efficacy.

A total of 20 patients (13 women and 7 men) with a median age of 59 years were enrolled in the study. All patients except one presented with a severe form of the disease, in almost all cases of a chronic nature. At the beginning of the study, all patients were using topical treatment (mainly glucocorticosteroids), and nine patients (45%) were also taking analgesics. Dupilumab was administered at the standard dose used in atopic dermatitis (i.e., 600 mg loading dose, followed by 300 mg every two weeks). At month 6, 18 patients (90%) responded to treatment, with 14 classified as having a very good response. The mean Dermatology Life Quality Index (DLQI) improved by a remarkable 15.5 points out of a possible 30. The frequency of topical treatment use decreased in seven patients (35%), and in nine patients (45%), this therapy was completely discontinued. Among the nine patients using analgesics at baseline, their use was reduced in 2 (22%) and completely discontinued in seven patients (78%). The number of hospitalizations decreased by 83%. After 6 months (mean treatment duration: 18.4 months), 16 of the 18 patients who initially responded to treatment maintained full efficacy, while two experienced relapses. Injection site pain occurred in four patients (20%), but resolved in all cases after switching from a prefilled syringe to a regular syringe. The results of this study show that dupilumab may be effective and well tolerated in the majority of patients with Hailey-Hailey disease. However, the study has several limitations, including its retrospective nature, potential selection bias resulting from recruitment in hospital settings, the inherently relapsing nature of the disease, and the influence of external factors (e.g., seasonal changes). These results highlight the need for double-blind, randomized trials to definitively confirm the efficacy and safety of dupilumab in the treatment of Hailey-Hailey disease [27].

Udupa et al. in a review paper on dupilumab treatment of acantholytic dyskeratotic disorders evaluated, among other things, the efficacy of dupilumab in patients with Hailey-Hailey disease. The group consisted of 15 patients with a longstanding (median duration: 12 years), treatment-

resistant form of this dermatosis. After dupilumab administration, a clinical response was achieved in all patients: complete remission of lesions was recorded in 46.6% of subjects, while partial remission was observed in the remaining 53.3%. The median time to improvement was 4.5 months. Similarly to earlier reports, the therapy was characterized by the absence of any significant adverse events. Additionally, one case of disease relapse after drug discontinuation and subsequent re-achievement of improvement after its reinstatement was noted, which demonstrates that dupilumab has a symptomatic effect and requires continuity of use [28].

## 4. Discussion

The data presented in this study indicate that bullous diseases- both of autoimmune origin (such as pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid) and genodermatoses (e.g., Hailey-Hailey disease)- represent a significant clinical challenge. This is due to their chronic course, tendency toward relapses of skin and mucosal lesions, and limitations of available therapeutic methods. Despite advances in the understanding of the pathogenesis of these conditions, treatment still largely relies on long-term immunosuppression. This is associated with the risk of numerous adverse effects and often does not allow for the achievement of lasting remission [6, 7].

One of the key issues addressed in this paper is the pathophysiological rationale for the use of dupilumab in bullous diseases. In bullous pemphigoid, there is strong evidence for the dominant role of type 2 inflammation, involving Th2 lymphocytes and the cytokines IL-4 and IL-13, which are responsible, among other things, for stimulating IgE production, eosinophilia, and pruritus [13]. The mechanism of action of dupilumab, consisting of blocking the IL-4Rα receptor, therefore appears to be directly targeted at key elements of the pathogenesis of bullous pemphigoid. In contrast, the pathomechanism of pemphigus is more complex and involves the participation of various T lymphocyte subpopulations (including Th1, Th2, and Th17) [19]. This suggests that the efficacy of dupilumab in this condition may be more limited or dependent on the individual immunological phenotype of the patient. Even greater doubts are raised by the use of this drug in Hailey-Hailey disease, which is based on a genetic defect in calcium transport [5]. In this case, the potential therapeutic effect may result more from the modulation of secondary inflammation than a direct effect on the primary cause of the disease.

Analysis of available clinical data indicates that the most evidence supporting the efficacy of dupilumab concerns bullous pemphigoid. The results of meta-analyses and the LIBERTY-BP ADEPT randomized trial suggest a significant reduction in disease activity, pruritus severity, and the possibility of achieving remission while simultaneously reducing glucocorticosteroid exposure [14–17]. Particularly significant is the fact that dupilumab- by blocking IL-4 and IL-13 signaling- affects the reduction of pruritus. This directly translates into an improvement in patients' quality of life, often to a greater extent than the reduction of skin lesions alone. However, it should be emphasized that despite promising results, some analyses (especially earlier ones) are based on retrospective studies and case series of limited methodological quality [15]. The high degree of data heterogeneity and the duplication of the same patient populations in various publications further limit the possibility of unambiguous interpretation of results.

In the context of pemphigus vulgaris and foliaceus, the available evidence is considerably more limited and is based almost exclusively on case reports and small clinical series [20–24]. Although these results often indicate the possibility of achieving remission and reducing glucocorticosteroid doses through the addition of dupilumab to treatment, caution must be exercised in their interpretation. Moreover, the lack of control groups makes it impossible to assess the true efficacy of the therapy and to exclude the influence of other factors (such as the natural course of the disease or the simultaneous use of other immunosuppressive drugs). An interesting aspect is the noted efficacy of dupilumab also in patients without features of type 2 inflammation (e.g., without eosinophilia or elevated IgE levels) [24], which suggests that its mechanism of action in these conditions may be more complex than originally assumed.

In the case of Hailey-Hailey disease, the available data also indicate high efficacy of dupilumab, particularly in reducing symptoms and improving quality of life [26–28]. However- similarly to pemphigus- most of the evidence comes from retrospective studies and small cohorts. An additional limitation is the lack of standardized tools for assessing disease severity, which makes it difficult to compare results between individual studies. It is also important to note that in many cases, disease relapse occurred after dupilumab discontinuation, suggesting that this treatment is symptomatic in nature and requires long-term continuity of use [28].

Another important aspect is the safety profile of dupilumab. Compared to classic immunosuppressive drugs (such as glucocorticosteroids or rituximab), it is characterized by a

more favorable safety profile and does not cause profound immunosuppression [7]. This is of particular importance in the population of elderly patients with bullous pemphigoid and in patients with contraindications to rituximab (e.g., active infections, malignancies) [20, 22]. However, this is not a completely adverse-effect-free therapy- the most commonly observed effects were conjunctivitis, injection site reactions, and eosinophilia [14, 17]. The long-term safety of dupilumab use in bullous diseases still requires further investigation.

In response to the research problems posed, it can be stated that dupilumab has a solid pathophysiological rationale primarily in bullous pemphigoid, and its use in other bullous diseases is promising but still experimental. The available data also suggest a significant steroid-sparing effect, which constitutes one of the most important clinical benefits of this therapy, particularly in the context of long-term treatment [16]. The safety profile of the drug appears favorable, but requires further evaluation in long-term studies.

In summary, dupilumab represents a promising therapeutic option in the treatment of bullous diseases, particularly bullous pemphigoid. Its use may contribute to reducing glucocorticosteroid exposure and improving patients' quality of life. However, the current state of knowledge, especially regarding pemphigus and Hailey-Hailey disease, is still limited and requires confirmation in rigorously designed randomized clinical trials.

## 5. Limitations

This paper, despite a comprehensive review of the available literature, has significant limitations that must be taken into account when interpreting the presented results. First and foremost, a substantial portion of the analyzed data (especially regarding pemphigus vulgaris and foliaceus and Hailey-Hailey disease) is based on single case reports, case series, and retrospective studies. The lack of randomization and control groups makes it impossible to unambiguously determine a causal relationship between drug use and the achieved clinical effect.

Another important limitation is the heterogeneity of the analyzed patient populations. The studies included patients with varying degrees of disease severity, disease duration, prior treatment, and different comorbidities, which makes it difficult to compare results and

generalize them. Additionally, in many cases, dupilumab was used in combination therapy with glucocorticosteroids or other immunosuppressive drugs, making it impossible to assess its true efficacy as monotherapy.

A significant methodological problem is also the lack of standardization of endpoints and tools for assessing treatment efficacy, particularly in Hailey-Hailey disease. The diversity of scales used and the subjective nature of some assessments (e.g., pruritus or quality of life) may affect the variability of results between studies. Furthermore, the observation period in most analyses was relatively short, which limits the ability to assess long-term efficacy and safety of the therapy.

In the case of meta-analyses concerning bullous pemphigoid, attention should be paid to the potential duplication of data from the same patients in various publications and the low methodological quality of some included studies. Despite the availability of one randomized trial (LIBERTY-BP ADEPT), the number of high-quality studies is still insufficient to formulate unambiguous clinical recommendations.

## 6. Conclusions

Dupilumab represents an important therapeutic option in the treatment of bullous diseases, particularly bullous pemphigoid, in which its use has a strong pathophysiological rationale associated with the dominance of type 2 inflammation. Available clinical data indicate that this drug effectively reduces disease activity, pruritus severity, and enables a reduction in the cumulative dose of glucocorticosteroids, which is of significant clinical importance- especially in the population of elderly patients.

In the case of pemphigus vulgaris and foliaceus and Hailey-Hailey disease, dupilumab demonstrates potential efficacy; however, its use in these conditions remains experimental at the current stage. The available evidence is limited and requires confirmation in studies of high methodological quality.

The safety profile of dupilumab is more favorable compared to classic immunosuppressive therapies, making it a particularly important option for patients with contraindications to

standard treatment, high risk of adverse effects, and children. Nevertheless, further evaluation of its safety in a long-term perspective is necessary.

## 7. Disclosure

### 7.1. Supplementary Materials.

No supplementary materials are available.

### 7.2. Author Contributions.

Conceptualization: Natalia Będkowska-Kuśmierek

Methodology: Sabina Zaborowska and Łukasz Starczewski

Software: Anna Złotnik

Validation: Kinga Krzysztofik and Olaf Wojcieszuk and Kamila Kamińska

Formal analysis: Paulina Pawlak and Matylda Będkowska-Kuśmierek

Investigation: Kamila Kamińska and Anna Złotnik and Natalia Będkowska-Kuśmierek

Resources: Adrianna Babik and Natalia Będkowska-Kuśmierek

Data curation: Łukasz Starczewski

Writing—original draft preparation: Natalia Będkowska-Kuśmierek and Kinga Krzysztofik and Adrianna Babik

Writing—review and editing: Natalia Będkowska-Kuśmierek and Kamila Kamińska

Visualization: Natalia Będkowska-Kuśmierek

Supervision: Natalia Będkowska-Kuśmierek

Project administration: Natalia Będkowska-Kuśmierek

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### 7.4. Institutional Review Board Statement.

Not applicable.

### 7.5. Informed Consent Statement.

Not applicable.

### 7.6. Data Availability Statement.

The study did not report any data.

### 7.7. Conflicts of Interest.

The authors declare no conflict of interest.

During the preparation of this work, the authors used ChatGPT for the purpose of language editing to improve clarity and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the substantive content of the publication.

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