Dupilumab: A Review of Present Indications and Off-Label Uses

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Abstract

Recent advances in our understanding of T2 inflammation have revealed more diseases in which T2 inflammation is involved. Dupilumab is a recently developed monoclonal antibody that blocks signaling of IL-4 and IL-13, both of which are crucial cytokines in the T2 response. New possible indications are increasingly explored and include skin diseases, such as prurigo nodularis, nummular eczema, allergic contact dermatitis, chronic hand eczema, spontaneous chronic urticaria, bullous pemphigoid, alopecia areata, and Netherton syndrome, as well as respiratory diseases, such as allergic bronchopulmonary aspergillosis, chronic eosinophilic pneumonia, and allergic rhinitis. In addition, eosinophilic gastrointestinal disorders, particularly eosinophilic esophagitis, and food allergy, are also research fields of interest. Here, we review published data and clinical trials examining the use of dupilumab in these disorders.

Key words: Dupilumab. Alopecia areata. Allergic bronchopulmonary aspergillosis. Allergic contact dermatitis. Chronic urticaria. Eosinophilic esophagitis. Cutaneous autoimmune bullous diseases. Food allergy.

Resumen

Los recientes avances en la comprensión de la inflamación T2 han mostrado otras enfermedades en las que la inflamación T2 está involucrada. El dupilumab es un anticuerpo monoclonal recientemente desarrollado que bloquea la transmisión de señales de IL-4 e IL-13, dos citocinas esenciales en la respuesta T2. Se están investigando posibles nuevas indicaciones, que incluyen enfermedades cutáneas, como el prurigo nodular, eccema numular, dermatitis alérgica de contacto, eccema crónico de manos, urticaria crónica espontánea, penfigoide ampolloso, alopecia areata y síndrome de Netherton, así como enfermedades respiratorias, como la aspergilosis broncopulmonar alérgica, neumonía eosinofílica crónica y rinitis alérgica. Además, las enfermedades gastrointestinales eosinofílicas, en particular la esofagitis eosinofílica y la alergia alimentaria, también constituyen áreas de investigación. En esta publicación se revisan los datos publicados y los ensayos clínicos que evalúan el uso de dupilumab en estas entidades.

Palabras clave: Dupilumab. Alopecia areata. Aspergilosis broncopulmonar alérgica. Dermatitis alérgica de contacto. Urticaria crónica. Esofagitis eosinofílica. Enfermedades ampollosas autoinmunes cutáneas. Alergia alimentaria.

Introduction: Type 2 Inflammation and Diseases

Type 2 (T2) inflammation is a particular type of inflammation in which type 2 helper T lymphocytes (T_H2) are the central cells of the adaptive immune response, with type 2 innate lymphoid cells (ILC2) probably being their "counterpart cell" in the innate immune response. Other important cells include B cells in the adaptive immune response and mast cells, basophils, and eosinophils in the innate response. Antigen-presenting cells (APCs), on the other hand, are at the boundary between both systems. Type 2 responses are involved in the defense against parasites, venoms, and toxins and in allergic diseases [1]. Type 2 responses are thought to be initiated in epithelial tissues with the production of alarmins (IL-25, IL-33, and thymic stromal lymphopoietin), which can activate both the innate and the adaptive immune responses [2]. Allergic diseases are based on IgE-dependent hypersensitivity to allergens in atopic individuals. Following the encounter with an allergen, APCs capture the allergen and process it into peptides. They migrate to the lymph node, where the allergen peptides are presented to naïve $CD4^+$ T cells. If CD4 T cells recognize the antigen in an IL-4–dominant milieu, they can transform into T_H2 cells, capable of producing the so-called type 2 cytokines (IL-4, IL-5, IL-9, and IL-13). Under the influence of IL-4, B cells undergo a class-switch process to produce allergen-specific IgE antibodies. Then, specific IgE binds to high-affinity IgE receptors (FcεRI) and low-affinity IgE receptors (FcεRI or CD23). The FcεRI located on the surface of effector cells such as mast cells and basophils arms, or sensitizes, them. Upon a second encounter with the allergen, mast cells and basophil degranulate, releasing preformed mediators (histamine, tryptase, chymase, proteoglycans) and rapidly synthesize new mediators, such as leukotrienes and prostaglandins. These mediators are responsible for symptoms. In addition, various cytokines, particularly IL-4 and IL-13, are later synthesized and released [3].

T2 inflammation can also present in the absence of specific IgE. Briefly, the alarmins released by the epithelium activate ILC2s, which in turn release large quantities of IL-5, IL-9, and IL-13, thus activating effector cells, such as eosinophils, M2 macrophages, basophils, and mast cells, and triggering the innate immune response [4]. Mast cells and basophils are additional sources of type 2 cytokines, particularly IL-4 and IL-13 [5]. Finally, there are significant functional interactions between ILCs and adaptive immunity [6].

Several diseases have been related to T2 inflammatory mechanisms, although they are not always associated with allergen-specific IgE. Thus, T2 inflammation is found in around 60% of patients with severe asthma and may or may not be accompanied by atopy [7]. In Europe and the US, most patients with chronic rhinosinusitis with nasal polyps (CRSwNP) present T2 inflammation [8,9]. Furthermore, in atopic dermatitis (AD), there is an intense inflammatory reaction with marked participation of T_H2 cells and cytokines [10]. Eosinophilic esophagitis (EoE) is a chronic progressive disease of the esophagus characterized by histologic and endoscopic changes, with infiltration of eosinophils and T2 inflammation [11].

IgE-mediated mechanisms have recently been described in other diseases, suggesting the involvement of T2 mechanisms [12]. Thus, antimyeloperoxidase IgE antibodies have been described in chronic spontaneous urticaria (CSU), which is frequently associated with thyroid autoimmunity [13]. Additionally, more than 200 autoantigens recognized by IgE have been detected in CSU patients, including IgE-anti-IL-24; IL-24 was shown to activate mast cells after preincubation with serum from IgE-anti-IL-24–positive patients [14]. This observation is further supported by the success of omalizumab in treatment of CSU [15], or even in inducible urticaria [16]. IgE autoantibodies have also been detected in bullous pemphigoid. Thus, a correlation between auto-IgE and disease severity has been reported in patients with specific IgE against the autoantigen BP180 [17], not only in serum, but also in the skin, bound to tissue-resident mast cells [18]. There are also reports of the efficacy of omalizumab in treating bullous pemphigoid [19]. Other allergic diseases include allergic rhinitis (AR) and food allergy.

IL-4 and IL-13 in T2 Inflammation

Three cytokines are critical in T2 inflammation, namely, IL-4, IL-5, and IL-13. IL5 is crucial in the development, growth, maturation, activation, and survival of eosinophils [20]. Eosinophils define eosinophilic asthma, where they play a significant role [21]. Thus, several biologics targeting IL-5, such as mepolizumab [22,23] and reslizumab [24], or targeting the α chain of the IL-5 receptor (IL-5RA), such as benralizumab [25], have proven efficacy in the treatment of eosinophilic types of asthma.

IL-4 and IL-13 have essential roles in T2 inflammation, significantly influencing the permeability of the epithelial barrier. Thus, in AD, IL-4 and IL-13 reduce filaggrin expression, leading to skin barrier defects [26]. Additionally, IL-4 and IL-13 inhibit the induction and expression of loricrin and involucrin, which are integral components of the stratum corneum, thus negatively impacting skin barrier function [27]. T_H2 cytokines can inhibit the expression of Toll-like receptors (TLRs), thus diminishing the host defense against infections[28].

In asthma, IL-4 and IL-13 produced by T_H2 cells [29] and ILC2s [30] can induce alterations in tight junction proteins, thus influencing epithelium permeability. In patients with allergic fungal rhinosinusitis and nasal polyposis, Wise et al [31] demonstrated that exposure of sinonasal epithelia to IL-4 and IL-13 altered intercellular junction proteins, reflecting increased epithelial permeability. It has also been shown that upregulation of the coagulation cascade and downregulation of fibrinolysis strongly induce abnormal fibrin deposition in the nasal mucosa, which is likely to be a primary driver of the formation of nasal polyposis [32]. In this sense, IL-4 and IL-13 contribute to remodeling and nasal polyp formation in CRSwNP by inducing alternative activation of macrophages to M2 macrophages [33], which are the main FXIII-A–producing cells in nasal polyposis. In addition, IL-13 suppresses the expression of tissue plasmin activator and induces factor XIIIA to promote the accumulation of fibrin mesh using thrombin and fibrinogen derived from plasma leakage [34]. In EoE, it has also been demonstrated that IL-13 decreases esophageal tight

junction barrier function, affecting the expression of multiple tight junction proteins (CLDN1, CLDN4, occludin, and ZO-1) and increasing permeability [35].

Other effects of IL-4 and IL-13 have been described. Thus, IL-4 induces B-cell class switching and increased IgE synthesis [36]. IL-4 is also essential in the development and maintenance of T_H2 responses [37,38]. Through the interaction with vascular cell adhesion molecule 1, IL-4 can direct migration of eosinophils to inflammatory loci [39]. Furthermore, IL-4 inhibits eosinophil apoptosis and induces eosinophil chemotaxis and activation by increasing expression of eotaxin [40]. In asthma, IL-13 causes goblet cell metaplasia and bronchial hyperreactivity and primes endothelial cells for upregulation of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1, thus influencing eosinophil egress to tissues [41].

In the esophagus, IL-13 seems to have a primordial pathogenic role. It induces CCL26, eotaxin-3, periostin expression, and recruitment of eosinophils and expression of CAPN14 [42]. CAPN14 is an esophageal protease that disrupts the esophageal barrier and enhances immune-mediated inflammation [43]. In asthma, IL-4 and, mainly, IL-13 are involved in remodeling. Thus, IL-13 induces goblet cell metaplasia, increases mucus production, promotes subepithelial collagen deposition, stimulates collagen type 1 production, induces the profibrotic molecule dipeptidyl peptidase 4 (DDP-4), and influences metalloproteinase expression [44]. In the esophagus, and unrelated to eosinophilia, IL-13 can induce tissue remodeling by promoting collagen deposition, angiogenesis, and epithelial hyperplasia [45]. In AD, it has recently been demonstrated that activation of signaling through IL-4Rα directly stimulates both mouse and human sensory neurons and that IL-4 enhances neuronal responsiveness to multiple pruritogens [46].

Dupilumab

Dupilumab is a recombinant IgG4 antibody targeting the α chain of the IL-4 receptor (IL-4Rα). There are 2 types of IL-4 receptors [47]: the type I receptor, which is formed by IL-4Rα and the γ chain (γC) and common to other IL receptors, and the type II receptor, which is constituted by IL-4Rα and the α-1 chain of IL-13 (IL-13Rα1). Given that IL-4 binds to IL-4Rα, it can bind both type I and type II receptors, whereas IL-13 binds to IL-13Rα1 and, consequently, can only signal through the type II receptor (Figure). The location of these receptors is different, explaining why IL-4 and IL-13 have overlapping and different effects. The type I receptor is principally found on hematopoietic cells and is the predominant IL-4 receptor expressed on T cells, basophils, mast cells, and mouse B cells [48]. The type II receptor is confined chiefly to nonhematopoietic cells. As these cells scarcely express the γ chain, IL-4 and IL-13 signaling essentially occur through the type II receptor [49]. Macrophages and dendritic cells express both types of receptors. Ligand binding induces the transphosphorylation and activation of associated JAK kinases (JAK1/JAK3 for the type-I receptor and JAK1/Tyk2 for the type-II receptor) [50]. This step is followed by a cascade of phosphorylation of specific tyrosine residues in the cytoplasmic domain of IL-4Rα, resulting in the activation of other signaling pathways, including STAT6, IRS/PI3K/mTORC2/AKT, SHC/MAPK, and Shp-1. Further signaling pathways include STAT3 activation via IL-13Ra1 and IRS2 regulation by Socs1/ubiquitin. The main effects of IL-4 and IL-13 have been described above. In a particular tissue, the relative and differential impact of IL-4 and IL-13 will depend on the location of IL-4 receptor expression, the primary receptor subtype, the relative abundance of each cytokine, and the presence of unique signaling pathways downstream of type I and type II receptors [49]. For example, type II airway receptor expression enables IL-13 to significantly influence epithelial cells, smooth muscle, airway resistance, goblet cell hyperplasia, and mucus production.

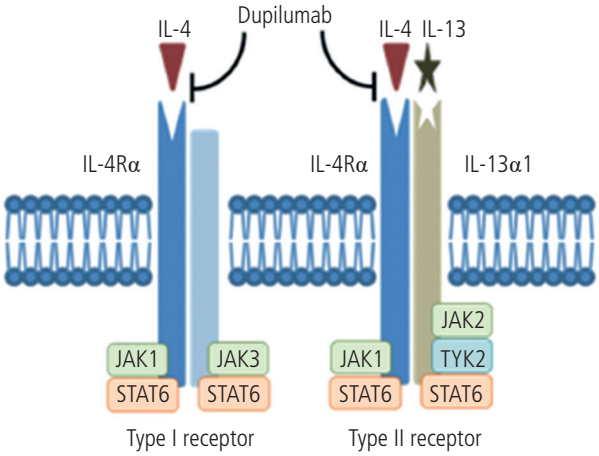

Figure. Mechanism of action of dupilumab. Dupilumab is a monoclonal antibody targeting IL-4Rα, thus inhibiting signaling of type I receptors (IL-4Rα/γC) and type II receptors (IL-4Rα/ IL-13Rα1) (reproduced from [47], with permission).

Approved Indications for Dupilumab

In the European Union, dupilumab has been approved for patients aged 12 years or over with moderate-to-severe AD and to treat severe asthma in patients aged 12 years or over whose disease is not adequately controlled by a combination of high-dose inhaled corticosteroids plus another medicine used for the prevention of asthma. Dupilumab is only for use in patients with T2 inflammation of the airways [51]. Very recently, dupilumab was also "indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery does not provide adequate disease control" [52]. Here, we briefly review the pivotal phase 3 studies on which these approvals were based.

In AD, the LIBERTY AD CHRONOS trial [53] demonstrated that long-term systemic treatment with dupilumab (300 mg every 2 or 4 weeks) added to topical corticosteroids in patients with moderate-to-severe AD significantly improved AD lesions based on an Investigator's Global Assessment 0/1 response and Eczema Area and Severity Index-75. Several other measures, including pruritus, anxiety and depression symptoms, and health-related quality of life, also improved. Additionally, the LIBERTY AD CAFÉ trial evaluated dupilumab 300 mg administered weekly or fortnightly to adults with an inadequate

response or intolerance to cyclosporine A or when this treatment was medically inadvisable, demonstrating an improvement in skin lesions, pruritus, and other symptoms of AD, including pain/discomfort and sleep disruption, symptoms of anxiety and depression, and health-related quality of life [54].

In asthma, the LIBERTY ASTHMA QUEST trial demonstrated that dupilumab 200 or 300 mg significantly reduced the annualized rate of severe asthma exacerbations and improved lung function, with more significant treatment effects in the form of increasing baseline levels of blood eosinophils and FeNO [55]. Additionally, in severe oral corticosteroid–dependent asthma, the LIBERTY VENTURE ASTHMA trial showed that adding dupilumab significantly reduced the dose of oral corticosteroids while simultaneously reducing the rate of severe exacerbations and improving lung function [56].

In CRSwNP, the LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 trials [57] evaluated dupilumab added to standard of care in adults with severe CRSwNP (300 mg biweekly for 24 weeks in both studies, plus 300 mg biweekly or monthly for the remaining 28 weeks in the SINUS-52 trial). At 24 weeks, in both studies, significant improvements were observed in the nasal polyp score, nasal congestion or obstruction, and the Lund-Mackay CT sinusitis score. The improvement observed at 4-8 weeks was maintained up to the end of treatment. Symptoms worsened after discontinuation of dupilumab at week 24 in SINUS-24 and continued to improve up to week 52 in SINUS-52. Furthermore, dupilumab resulted in substantial reductions in the need for systemic corticosteroids and surgery. There was also a significant improvement in the 22-item Sino-Nasal Outcome Test score and in the University of Pennsylvania Smell Identification Test. In patients with concomitant asthma, a significant improvement in lung function and asthma control was observed at week 24.

Use of Dupilumab in Other Diseases

Cutaneous Diseases

Since its approval, dupilumab has proven efficacious in patients with AD and as off-label medication in chronic dermatological conditions [58-60]. Although most data are from case reports and small case series, the pathophysiology of these dermatoses and the mechanism of action of dupilumab suggest the possibility of new indications for this drug. One clinical trial on alopecia areata has recently been concluded [61], and more clinical trials are currently underway on prurigo nodularis [62,63], allergic contact dermatitis [59,64], chronic pruritus [65], chronic hand eczema [66,67], CSU [68,69], cholinergic urticaria [70], chronic inducible cold urticaria [71], bullous pemphigoid [72], nummular eczema [73], localized scleroderma [74], and Netherton syndrome [75]. However, further confirmatory studies are needed.

Prurigo nodularis

Chronic prurigo nodularis is characterized by pruritic papules and nodules, which are usually resistant to standard treatment and significantly affect quality of life. Silvestre et al [76] proposed considering prurigo nodularis as a clinical form of AD in adults. However, prurigo nodularis is currently not an indication for dupilumab. Published clinical cases and the case series (Table 1) bring together 118 patients diagnosed with chronic prurigo nodularis [77-96] and include patients with and without a history of atopy. Only one involved a child. All patients received dupilumab at the recommended dose for treatment of AD, and previous treatments with topical and systemic immunosuppressants did not demonstrate efficacy, caused adverse reactions, or were contraindicated. The disease generally improved in all the patients included, with reductions in the intensity of pruritus and in the number and size of the lesions. Pruritus generally responded earlier than lesions, and both continued to decrease throughout the treatment. Nevertheless, even if they responded early, the latency periods for the reduction in pruritus and nodules varied widely from the start of treatment with dupilumab and were strongly determined by the visit interval. Treatment was efficacious earlier in patients with a history of atopy. No differences were observed in the final response rate between atopic and nonatopic patients [84,85].

Husein-ElAhmed et al [97] reviewed data on 45 patients from 11 articles and reached similar conclusions, emphasizing the importance of 2 early signs of improvement as predictors of the future response to dupilumab. The authors suggested that complete remission can be expected when the patient perceives an improvement at around 8 weeks of treatment and a 50% reduction on the Numerical Rating Scale before dupilumab therapy is matched. Conversely, when improvement occurs after 12 weeks or more or the 50% reduction is not achieved, a complete response is unlikely.

The limitations of research on prurigo nodularis to date are evaluation of efficacy based on different tools at different times, the short-term observation period considered, and the small cohort of treated patients, allowing only a descriptive analysis of the data. Therefore, standardized, validated parameters to assess the effects of treatment and well-designed clinical trials are compulsory.

In any case, the effect of dupilumab on skin lesions, itching, sleeplessness, and quality of life in prurigo nodularis suggests that the T_H2 pathway likely mediates itching in this dermatosis.

Nummular eczema

Like prurigo nodularis, nummular eczema is currently considered one of the clinical forms of AD [76], although, alone, it is not an inclusion criterion for AD clinical trials. The published case series evaluating the effect of dupilumab in nummular eczema include those of Tavecchio et al [93] and Patruno et al [98], who reported a good response in clinical improvement and impact on quality of life in 8 and 30 patients, respectively, with the nummular eczema–like AD phenotype. On the other hand, dupilumab has also been successful in patients with nummular dermatitis and no history of AD [99], suggesting that the T_H2 axis may be involved in this dermatosis in patients without AD.

Allergic contact dermatitis

Traditionally, T_H1 and T_H17 cells were thought to be the primary effector cells that cause tissue damage in allergic contact dermatitis. Cellular and molecular studies of patch

Table 1. Treatment With Dupilumab in Prurigo Nodularis: Published Case Reports and Case Series

Reference	No. of patients	Age, y	History of atopy	Latency period until improvement	Previous treatments
Almustafa et al [77]	3	41-52	Yes	2-8 wk (itch) / later (nodules)	tCS, Pho, CsA, Gb
Beck et al [78]	3	50s-70s	NS	4-12 wk (itch and nodules)	CS, AH, Dxp, Gbp, Pho, Cry, Mup, CsA, dronabinol
Calugareanu et al [79]	1	30	Yes	12 wk (itch and nodules)	CS, Cry, AH, Pho, Dap, Mtx, Thl, CsA
Ferrucci et al [80]	11	19-88	Yes	4 wk (itch and nodules)	tCS, tCI, CS, CsA, Mtx
Mollanazar et al [81]	4	30s-50s	Yes (x1) / No (x3)	2-4 wk (itch) / NS (nodules)	tCS, tCI, Mtz
Rambhia et al [82]	2	40-53	No	4 wk (itch) / NS (nodules)	tCS, CS, AH, Pho, Mtx, Ust, Mpm, Dxp, Etn, Thl, Lnl, Ntx, Gb, Apr, Tfb
Tanis et al [83]	1	43	NS	8 wk (itch and nodules)	tCS, CsA, Pho, Mtx
Calugareanu et al [84]	16	56 (median)	Yes (x7) / No (x9)	12 wk (itch and nodules)	tCS, Pho, Mtx, CsA, Thl
Chiricozzi et al [85]	27	23-83	Yes (x18) / No (x9)	4 wk (itch) / NS (nodules)	CS, CsA, Pho, Mtx, Azt
Criado et al [86]	1	87	Yes	4 wk (itch) / 16 wk (nodules)	CS, AH, CsA, Mtx, PreG, Mtz
Fachler et al [87]	1	9	No	2 wk (itch) / 4 wk (nodules)	tCS, AH, Pho, CsA, Mtx,
Giura et al [88]	1	85	No	1 week (itch) / 4 wk (nodules)	tCS, CS
Holm et al [89]	3	42-57	No	NS	tCS, tCI, Pho, AH, Mtx, Thl, Azt, AB, cannabidiol
Kovács et al [90]	1	80	Yes	2 wk (itch) / later (nodules)	tCS, AH, Pho, tCI, Mtz, Gb, Prx, CsA, Mtx, Nlx, Ntx
Napolitano et al [91]	9	31-63	Yes	16 wk (itch and nodules)	tCS, AH, Pho, CsA, Mtx
Romano [92]	1	61	No	4 wk (itch and nodules)	NS
Tavecchio et al [93]	18	NS	Yes	4 wk (itch and nodules)	tCS, tCI, CS, CsA, Azt, Mtx
Tilotta et al [94]	11	62-78	Yes	4 wk (itch and nodules)	tCS, AH, CS, CsA
Wieser et al [95]	3	65-66	Yes (x1) / No (x2)	4-28 wk (itch and nodules)	tCS, AH, CS, Mtx, Gb, AB, tCI, Mup
Winkler et al [96]	1	83	No	NS	tCS, tCI, AH, Gb, Pho, CS, CsA, Mtx

Abbreviations: AB, antibiotics; AH, antihistamines; Apr, apremilast; Azt, azathioprine; CS, systemic corticosteroids; CsA, cyclosporine; Cry, cryotherapy; Dap, dapsone; Dxp, doxepin; Etn, etanercept; Gb, gabapentin; Lnl, lenalidomide; Mpm, mycophenolate mofetil; Mtx, methotrexate; Mtz, mirtazapine; Mup, mupirocin; Nlx, naloxone; NS, not specified; Ntx, naltrexone; Pho, phototherapy; Prx, paroxetine; tCS, topical corticosteroids; tCI, topical calcineurin inhibitors; Tfb, tofacitinib; Thl, thalidomide; Ust, ustekinumab.

test reactions have demonstrated that cytokine responses cannot be generalized across allergens and instead are hapten-specific, with both T_H1 and T_H2 responses observed. For example, nickel is a known potent inducer of innate and adaptive immunity, with the latter predominately involving T_H1- and T_H17-mediated pathways. In contrast, fragrances and rubber are thought to activate a predominately T_H2-mediated pathway [100,101]. Therefore, for specific allergens eliciting allergic contact dermatitis, immune mechanisms may more closely overlap those of AD than of other allergens, suggesting that dupilumab could be useful in treating recalcitrant or severe allergic contact dermatitis. The lack of systemic treatments indicated for widespread recalcitrant contact dermatitis has led to the off-label use of dupilumab.

Table 2. Effect of Dupilumab on Patch Tests Results

Reference	No. of patients	Predupilumab positive patch tests	Positive patch tests during treatment with dupilumab
Puza et al [109]	1	Formaldehyde (irritant?)	Methylisothiazolinone (+) Formaldehyde (irritant)
Hoot et al [110]	1	Not specified	Lanoline (+/–) Black rubber mix (+) Carba mix (+/–) Triethanolamine (+) Bacitracin (+++) Neomycin (+++)
Raffi et al [111]	1	Nickel sulfate (++) Bronopol (++) Methylisothiazolinone (+++) Compositae mix (+) Hydroperoxides of linalool (++)	Bronopol (++) Methylisothiazolinone (+++)
Stout et al [112]	7	Lanolin Propolis Fragrance mix I Citral Farnesol Fragrance mix II Amyl cinnamyl alcohol Anise alcohol Benzophenone-4 Neomycin sulfate Bacitracin Gentamicin sulfate Ethylenediamine dihydrochloride Naphthyl mix N,N9-Diethylthiourea Mixed dialkyl thioureas Nickel sulfate hexahydrate Thimerosal Phenyl mercuric acetate Ethyl cyanoacrylate Amidoamine Sorbitan sesquioleate Ammonium persulfate	Lanolin Propolis Fragrance mix I Benzophenone-4 Neomycin sulfate Bacitracin Nickel sulfate hexahydrate Formaldehyde Diazolidinyl urea Potassium dichromate Hydroperoxides of linalool Isoeugenol Musk xylene Jasmine synthetic Benzyl salicylate Cinnamal Methyl dibromo glutaronitrile/phenoxyethanol Cocamide DEA
Zhu et al [113]	1	Nickel sulfate hexahydrate (++) Methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) (+++) Methylisothiazolinone (MI) (+++) 2-n-octyl-4-isothiazolin-3-one (+) 4,4-dithiodimorpholine (+)	Nickel sulfate hexahydrate (+) Methylisothiazolinone (MI) (+++)
Raffi et al [114]	23	(125 allergens tested)	(See text)

Case reports and small case series have shown that patients with refractory allergic contact dermatitis to specific allergens, for which contact avoidance was not possible, improved after starting dupilumab. With or without AD, the patients responded similarly with improvement in itching and skin lesions after 2 weeks to 6 months [102-107]. In contrast, 1 patient developed recall dermatitis at a colophony patch test site on starting treatment with dupilumab, suggesting that dupilumab may unbalance the T_H1/T_H2 response to certain contactants [108].

Another question addressed by various authors is that of the effect of dupilumab on patch test results. Case reports [109,110] have described positive patch tests with various allergens (methylisothiazolinone, lanoline, black rubber mix, carba mix) in patients receiving dupilumab for AD, thus showing that the reaction was not inhibited by blocking the IL-4 and IL-13 receptor. Other case reports and case series [111-114] compared patch testing results before and during dupilumab therapy for AD (Table 2). Raffi et al [114] recently published a retrospective review comparing the results of patch tests performed before and after initiation of dupilumab for treatment of AD (n=23) and found that a minority of patch test reactions were "missed" with dupilumab (10.4%). Among the 125 allergens tested,

those involved in this loss of sensitization were propylene glycol, Amerchol, dimethylaminopropylamine, balsam of Peru, fragrance mix, sulisobenzone, phenyl benzimidazole-5-sulfonic acid, vanadium (III) chloride, phenylmercuric acetate, iodopropynyl butylcarbamate, bacitracin, and tosylamide/formaldehyde resin. In the remainder, the positive patch test result was questionable (38.4%) or persistent (51.2%). Therefore, dupilumab does not appear to exert a reliable or uniform buffering effect on patch test results. Its effect appears to be specific to some allergens but not to others. In this sense, Dhingra et al [100] suggested that the immune response to contactants would vary, involving different molecular pathways for different allergens. Thus, given the variable response observed in patch testing, this should be performed before considering dupilumab in recalcitrant and resistant allergic contact dermatitis.

Chronic hand eczema

Chronic hand eczema is a heterogeneous dermatosis with multiple etiologies, clinical patterns, and limited therapeutic options. Its pathogenesis is unclear, although it involves IL-4 and IL-13 signaling, among other mechanisms [115]. Thus, it would be expected that dupilumab could be as useful as in AD, at least in some cases of chronic hand eczema. In trials studying the effect of dupilumab in AD, patients with dermatitis limited to the hands are excluded because the affected area is below 10% of the body surface. However, case reports and small case series have reported that AD patients with concomitant hand eczema who received dupilumab experienced significant improvements in hand eczema, as measured by the hand severity index and quality of life instruments. These reports encompass various types of hand eczema, including contact [116,117], atopic [117,118], vesicular [119], dyshidrotic [120], hyperkeratotic [121], and irritant hand eczema [117,121,122], most of which improve significantly (Table 3). The main limitation of published series is the risk of misclassification bias, given the diversity of the criteria used to classify the disease.

Chronic urticaria

CSU is a common skin disorder of unknown cause characterized by itchy, evanescent red wheals that appear

Table 3. Effect of Dupilumab in Chronic Hand Eczema

Reference	No. of patients	Age, y	History of atopy	Onset of improvement	Previous treatments
Oosterhaven et al [116]	1	50s	Yes	4 wk	tCS, Pho, CS, alitretinoin, CsA, Azt, Myc, tCI, Mtx
Oosterhaven et al [117]	47	20-69	Yes	4 wk	CsA, CS, Mtx, Azt, alitretinoin, Myc, Mpm, tCI
Zirwas [118]	3	48-72	Yes	6-12 wk	tCS, tCI, CS, Thl, Mtx, Myc, CsA, Apr, Utk,
Halling et al [119]	1	67	No	2 wk	tCS, Pho, Mtx, Azt, CsA
Waldman et al [120]	15	32-76	No	NS[a]	tCS; at least 1 oral immunosuppressive, phototherapy, or both
Loman et al [121]	3	47-65	Yes (1x) / No (2x)	4 wk (2x) / only pruritus and quality of life (1x)	tCS, alitretinoin, acitretin, CsA, Mtx, Azt
Zhu et al [122]	1	43	No	4 wk	tCS, CS, Pho, acitretin, Mtx

Abbreviations: Apr, apremilast; Azt, azathioprine; CS, systemic corticosteroids; CsA, cyclosporine; Mpm, mycophenolate mofetil; Mtx, methotrexate; Myc, mycophenolic acid; Pho, phototherapy; tCI, topical calcineurin inhibitors; tCS, topical corticosteroids; Ust, ustekinumab.
[a]NS, not specified. All patients demonstrated at least partial response (erythema and pruritus); 40% had complete clearance.

Table 4. Effect of Dupilumab on Chronic Urticaria

Reference	No. of patients	Age, y	History of atopy	CSU/CINDU	Onset of improvement	Previous treatments
Lee et al [123]	6	18-50	Yes	CSU	Within 3 mo	Ketotifen, gabapentin, montelukast, ranitidine, bilastine, omalizumab
Ferrucci et al [124]	1	28	Yes	Cold induced urticaria	1 mo	Cetirizine, prednisone, omalizumab, ciclosporin
Föhr et al [125]	1	21	Yes	CSU/ cholinergic urticaria	Within 26 wk	Antihistamine, omalizumab

Abbreviations: CSU, chronic spontaneous urticaria; CINDU, chronic inducible urticaria.

for more than 6 consecutive weeks. It is often of concern to patients and physicians owing to impairment of quality of life and resistance to treatments. Although omalizumab is currently the treatment of choice for antihistamine-resistant CSU and chronic inducible urticaria, some case reports and case series support dupilumab as an emerging treatment when omalizumab fails (Table 4). Thus, Lee et al [123] described 6 patients with AD and refractory CSU who did not respond to 300 to 600 mg of omalizumab but responded favorably to dupilumab within 3 months of treatment.

Regarding chronic inducible urticaria, a case of cold urticaria in the context of severe AD has also been reported. The patient improved dramatically after 1 month of dupilumab therapy, and the ice cube test became negative [124]. Similarly, in the case of a patient diagnosed with CSU with angioedema, cholinergic urticaria, and AD, treatment with omalizumab resulted in an improvement in urticaria, but not in AD. The use of dupilumab resulted in complete healing of AD, complete remission of CSU and satisfactory control of cholinergic flare-ups [125].

Cutaneous autoimmune bullous diseases

In recent years, given the supposed central role of the type 2 response in the pathogenesis of bullous autoimmune skin diseases (bullous pemphigoid, mucous pemphigoid, and pemphigus vulgaris), some authors have proposed anti-IL-4Rα as a potential therapy for these diseases [126,127].

The few clinical cases and case series published on this topic are related to bullous pemphigoid, which more frequently affects elderly patients whose therapeutic options are limited. Almost all patients experienced a significant improvement, first in pruritus and later in bullous pemphigoid lesions [128-130] (Table 5). In the only multicenter case series reported, disease remission or satisfactory response was achieved in 92.3% of patients, and total clearance of bullous pemphigoid was achieved in 53.8% of patients [130].

Alopecia areata

Alopecia areata or its advanced form, alopecia universalis, and AD are common skin diseases that may coexist in the same patient, with AD being a predictor of poor prognosis. Renert-Yuval et al [131] provided an overview of activated immune pathways in alopecia areata, in which they analyzed overexpression of IL-4 and IL-13 and possible therapeutic modalities, including dupilumab. Recently, cases of alopecia areata [132-140] and alopecia universalis [135,140-147] have been reported to heal during treatment with dupilumab for AD. Therefore, this dual efficacy of dupilumab for AD and alopecia areata/alopecia universalis may be explained by their shared immunopathogenic mechanisms. However, paradoxically, new-onset alopecia areata [147-152] and reactivation of alopecia areata [152,154] have been reported, thus pointing to a temporal relationship between dupilumab and alopecia areata.

Netherton syndrome

Netherton syndrome, ichthyosis linearis circumflexa, is a rare autosomal recessive disorder caused by loss-of-function mutations in the *SPINK5* gene, thus compromising the function of the serine protease inhibitor LEKTI-1. It is characterized by congenital ichthyosis, hair abnormalities, and atopy and has limited treatment options. Two children [155] and 2 adults [156,157] significantly improved their ratings of overall disease severity and quality of life. In contrast, another case report of an adolescent showed only temporary improvement during the first 6 weeks of treatment with dupilumab [158].

Pruritus

Eriksson et al [159] recently published an extensive review of chronic pruritus and the complex interactions between the skin and the immune and nervous systems, highlighting the involvement of type 2 cytokines (IL-4, IL-13, and IL-31) as critical regulators of itch. Therefore, pruritus in both atopic and nonatopic individuals has been reported to improve with dupilumab for various types of chronic refractory itch, such as lichen planus, genital itching, uremic itching, idiopathic itching, and eosinophilic dermatosis of hematological malignancies [160-162]. In addition, isolated case reports show the beneficial effect of dupilumab in various skin disorders and diseases affecting the skin, such as eosinophilic annular erythema (with the resolution of all lesions and pruritus [164,165]), keloids [166], pruritic epidermolysis bullosa [167], hypereosinophilic syndrome [168], and cutaneous T-cell lymphoma (mycosis fungoides) [169].

Table 5. Effect of Dupilumab in Bullous Pemphigoid

Reference	No. of patients	Age, y	History of atopy	Onset of improvement with dupilumab	Previous treatments
Kaye et al [128]	1		Yes	1 wk (itch)/12 wk (blisters)	tCS, Pho, CsA, Gb
Seidman et al [129]	1	89	NS	2 wk (itch)/7 wk (blisters)	CS, AH, Dxp, Gb, Pho, Cry, Mup, CsA, dronabinol
Abdat et al [130]	13	53-91	Yes	12 wk (itch and nodules)	CS, Cry, AH, Pho, Dap, Mtx, Thl, CsA

Abbreviations: AH, antihistamines; CS, systemic corticosteroids; CsA, cyclosporine; Cry, cryotherapy; Dap, dapsone; Dxp, doxepin; Gb, gabapentin; Mtx, methotrexate; Mup, mupirocin; NS, not specified; Pho, phototherapy; tCS, topical corticosteroids; Thl, thalidomide; Ust, ustekinumab.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a T_H2 hypersensitivity reaction to *Aspergillus fumigatus* antigens, which colonize the airways of susceptible persons, such as asthmatics and patients with cystic fibrosis [170]. This results in bronchial mucoid impaction secondary to eosinophilic infiltration, the elevation of total IgE and specific IgE against *Aspergillus fumigatus*, and peripheral blood and sputum eosinophilia. Bronchiectasis and fibrosis are irreversible complications of ABPA. Therapy is directed at mitigating the allergic inflammatory response. For severe asthmatics with ABPA, treatment has been limited to systemic corticosteroids and antifungal agents [171,172]. However, many patients do not respond, present frequent exacerbations, or develop adverse effects to treatment [171,173]. In recent years, several studies and case reports have shown the efficacy of biologics such as omalizumab, mepolizumab, and benralizumab in the treatment of ABPA [174-177].

The biologic characteristics of ABPA suggest a role for anti-IL-4/13 therapy. A specific role for IL-4R blockade has been suggested, based on the increased sensitivity of T_H2 cells to IL-4 and upregulation of CD23 on B cells in patients with ABPA [178]. Furthermore, *Aspergillus fumigatus* induces the *Muc5ac* gene by stimulating epidermal growth factor receptors [179]. *Muc5ac* is one of the mucin genes that contribute to the formation of mucus plugs in the bronchi. IL-13 is known to upregulate *Muc5ac* production, and the inhibition of IL-13-induced periostin attenuates *Muc5ac* expression in airway epithelium [180]. In a murine model of ABPA, Dietschmann et al [181] recently showed that T cells released amounts of IL-4, IL-5, and IL-13 upon stimulation with *Aspergillus fumigatus*.

Corren et al [182] performed a post hoc analysis of a phase 3 study (Liberty Asthma Quest) [183], including 18 patients with serologic evidence of ABPA (baseline serum total IgE >10 000 IU/mL, serum specific IgE to *Aspergillus fumigatus* >0.35 IU/mL, and blood eosinophilia >500/mL). Dupilumab reduced severe exacerbation rates by 81%. The analysis reported mean baseline FEV_1 values of 2.00 L. After treatment, FEV_1 was 2.37 L and 2.51 L at weeks 24 and 52, respectively. Dupilumab significantly reduced total IgE, specific IgE to *Aspergillus fumigatus*, and FeNO.

Ramonell et al [184] published a case series including 3 patients (2 women and 1 man) with a median age of 51 years. One patient had been receiving treatment with mepolizumab, and another had been receiving both omalizumab and mepolizumab with no significant improvement. The authors reported mean baseline FEV_1 values of 1.98 L (range, 1.51-2.75) and 2.33 L (range, 2.18-2.82) after 3-6 months of treatment. A decrease in IgE values and eosinophil counts was also observed. All 3 patients discontinued systemic corticosteroids after treatment with dupilumab. Early eosinophilia was observed in 2 patients, 1 of whom experienced an asthma exacerbation, for which concomitant corticosteroids were administered, without treatment having to be stopped.

A further 2 cases that demonstrate the beneficial effects of dupilumab in patients with ABPA were recently published [185,186]. Mümmler et al [185] reported the case of a 49-year-old woman with severe asthma that remained uncontrolled despite therapy with oral corticosteroids, benralizumab, and omalizumab. Switching to dupilumab led to complete resolution of pulmonary symptoms, increased FEV_1, reduced IgE, and withdrawal of oral corticosteroids. In the case reported by Tashiro et al [186], a 72-year-old woman with ABPA was treated with dupilumab before receiving oral corticosteroids to prevent related adverse events owing to her history of cataract and infection by nontuberculosis mycobacterium. After 3 months of treatment, her symptoms had resolved, infiltrations on the chest computed tomography scan had disappeared, and pulmonary function and FeNO values improved significantly. Serum total IgE and specific IgE to *Aspergillus* were decreased. Analysis of several cytokines and chemokines revealed a significant decrease in CD40L; CD40 is associated with T-cell activation, with production of IL-4 and induction of IgE production from B cells. The authors suggest that CD40L might be a useful biomarker of the pathophysiology of ABPA.

Although the effects of dupilumab seem beneficial in the cases analyzed, further large-scale studies are needed to explore the role of dupilumab in the treatment of ABPA.

Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia is an eosinophilopoietic process in the airway modulated by type 2 cytokines such as IL-4 and IL-13. Fowler et al [187] reported a case of chronic eosinophilic pneumonia in an 11-year-old African American girl in whom treatment with pulse methylprednisolone and daily cyclosporine to achieve clinical remission resulted in modest improvement of symptoms. The addition of 300 mg dupilumab every 2 weeks caused significant clinical and radiographic improvements. Cyclosporine was subsequently weaned without recurrence of symptoms, and the patient remained symptom-free, with marked improvement in her chest x-ray findings for over 12 months.

Eosinophilic Gastrointestinal Disorders

Eosinophilic gastrointestinal disorders are primary T_H2-driven disorders characterized by eosinophilic inflammation of gastrointestinal tissues [188]. The most prevalent and best-known form is EoE. The disease is characterized by infiltration of the esophageal mucosa by ≥15 eosinophils per high-power field and manifests as esophageal dysfunction, mainly dysphagia and food impaction. Eosinophilic gastroenteritis typically involves the stomach and small bowel, producing symptoms in both the upper and the lower digestive tract [189]. Finally, eosinophilic colitis, ie, infiltration of eosinophils throughout the colon, typically presents as abdominal pain and diarrhea [189].

The prevalence of EoE has increased during the last decade, especially in Western countries [190]. In most cases, the natural course of the disease appears to be progressive, leading to esophageal remodeling. Currently, the management of EoE is focused on controlling inflammation and tissue remodeling with corticosteroids and proton-pump inhibitors and recommendation of an elimination diet to avoid antigenic

stimulation [191]. Nevertheless, endoscopic dilation of the fibrostenotic esophagus using medical and dietary therapies may be necessary in uncontrolled disease. Thus, medical treatments that prevent submucosal fibrosis and tissue remodeling are of considerable interest.

Several biologic agents are being investigated for the management of EoE. EoE is frequently associated with allergic IgE-mediated disorders such as AR, asthma, and food allergy. Therefore, omalizumab, an anti-IgE monoclonal antibody, was assessed as treatment for 30 adult patients, although it did not improve symptoms compared with placebo, and eosinophils counts were not altered in biopsy samples of patients treated with omalizumab [192]. IL-5 has a central role in the proliferation and maturation of eosinophils and is therefore a therapeutic target in EoE. The IL-5 blockers mepolizumab [193,194] and reslizumab [195] have been tested, although neither was superior to placebo in terms of symptom relief. Benralizumab, an antibody that blocks IL-5Ra, is being investigated in an ongoing placebo-controlled trial (NCT03473977) in eosinophilic gastritis and gastroenteritis [196].

IL-13 plays a central role in EoE. Expression of the *IL13* gene is upregulated in the esophageal epithelium of EoE patients [197]. Overexpression of esophageal *IL13* induces expression of CCL26, eotaxin-3, and periostin, as well as eosinophilic recruitment by upregulation of an eosinophil chemokine and calpain 14 (CAPN14) [42]. CAPN14 is a protease found in the esophagus that disrupts the esophageal barrier, thus enhancing immune-mediated inflammation [43]. IL-13 downregulates the expression of desmoglein-1, filaggrin, epidermal differential complex, and involucrin, which are essential proteins for epithelial integrity and barrier function [42]. In addition, IL-13 induces tissue remodeling by promoting collagen deposition, angiogenesis, and epithelial hyperplasia [42].

Dupilumab has received orphan drug status for the treatment of EoE from the Orphan Drug Designation program of the United States Food and Drug Association. Dupilumab has been tested for the treatment of EoE. The results of a 12-week phase 2, randomized, double-blind, placebo-controlled clinical trial in patients with moderate-to-severe EoE were recently published [198]. Overall, 47 adult patients with moderate-to-severe EoE were randomly allocated to receive dupilumab (600-mg loading dose followed by 300 mg weekly) or placebo. At week 10, a significant improvement in swallowing ability was reported by patients who received dupilumab compared with placebo (45% vs 19% improvement from baseline in the Straumann Dysphagia Symptoms score). At week 12, dupilumab reduced the peak esophageal intraepithelial eosinophil count by a mean of 86.8 eosinophils per high-power field (reduction of 107.1%; $P<.0001$ vs placebo). Endoscopic and histological activity improved significantly among treated patients, and endoscopic esophageal distensibility increased by 18% compared with placebo. An ongoing phase 3 randomized clinical trial is assessing the long-term efficacy and tolerability of dupilumab 300 mg every week or every 2 weeks compared to placebo in adults and adolescents with EoE (NCT03633617) [199]. Dupilumab is also being investigated for use in eosinophilic gastritis and eosinophilic gastroenteritis in a phase 2 trial (NCT03678545) [200]. Patients receive 600 mg once, followed by 300-mg doses of dupilumab or placebo every 2 weeks for a total of 6 injections, followed by an open-label phase in the case of response.

Food Allergy

T_H2-driven inflammatory responses are characteristic of food allergy [201]. Several studies have found increased levels of the T_H2-associated cytokines IL-4, IL-5, and IL-13 in food-allergic patients [202,203]. Additionally, mutations in *IL4RA* and *IL13* are associated with an increased risk of food allergy, thus highlighting the importance of T_H2 cytokine signaling in food allergy [204,205].

Recently, Rial et al [206] reported the case of a 30-year-old woman with a history of severe AD, AR, asthma, and food allergy related to corn and pistachio. The patient received dupilumab for severe AD. Both pistachio and corn were subsequently tolerated during an open food challenge after 3 months of therapy. This was the first report of a patient treated with dupilumab for food allergy.

Three ongoing randomized placebo-controlled phase 2 clinical trials are evaluating dupilumab in peanut allergy. One of these studies is evaluating dupilumab in monotherapy (NCT03793608) [207]. The study's primary objective is to assess the tolerability of peanut in pediatric patients (6-17 years old) treated with dupilumab in monotherapy. Tolerability is defined as the proportion of patients who safely pass a double-blind placebo-controlled food challenge (DBPCFC) at week 24. Another study is evaluating the efficacy of dupilumab as an adjunct therapy to peanut oral immunotherapy (NCT03682770) [208]. The primary objective is to assess whether dupilumab improves desensitization after up-dosing, with improvement defined as an increase in the proportion of participants who pass a post–up-dosing DBPCFC at visit 16. Another randomized phase 2 trial anticipated in patients with multiple food allergies, including peanut, aims to compare the safety and efficacy of dupilumab, omalizumab, or both as an adjunct in multifood oral immunotherapy (NCT03679676) [209]. The total population will be 110 participants aged 6 to 25 years with a history of multiple food allergies to 2 or 3 different foods, including peanut, food allergen–specific IgE levels, and positive skin prick test results. Enrolled participants must react positively during DBPCFCs at or before the 300-mg (444 mg cumulative) dosing level of 2 or 3 allergens, of which 1 must be peanut. There will be 3 study cohorts; all will be double-blinded. Cohort A (50 participants) will be treated with omalizumab for 8 weeks followed by 24 weeks of treatment with placebo. Cohort B (50 participants) will be treated with omalizumab for 8 weeks, followed by 24 weeks of treatment with dupilumab. Cohort C (10 participants) will be treated with placebo for 8 weeks followed by 24 weeks' treatment with dupilumab. All cohorts will receive multifood allergen oral immunotherapy.

Another ongoing randomized placebo-controlled phase 2 clinical trial is evaluating dupilumab as an adjunct to milk oral immunotherapy (NCT04148352) [210]. This phase 2, multicenter, randomized, double-blind, parallel-group, 2-arm study is investigating approximately 40 persons aged 4 to 50 years who are allergic to cow's milk. The primary objective

is to assess whether dupilumab as an adjunct to milk oral immunotherapy compared to placebo improves the safety of milk oral immunotherapy and rates of desensitization, with improvement defined as an increase in the proportion of persons who pass a DBPCFC with at least 2040 mg milk protein (cumulative) at week 18. It is not yet recruiting patients.

Dupilumab may benefit patients with multiple coexisting allergic diseases. In trials examining moderate-to-severe AD treated with dupilumab, 35% to 61% of adolescents had food allergy [211,212]. One study on adolescents with atopic dermatitis found improved asthma symptoms, AR symptoms, and IgE levels for cow's milk, egg white, peanut, and aeroallergens [212]. An ongoing observational prospective study (NCT04462055) is analyzing patients with moderate-to-severe AD who are candidates for treatment with dupilumab and have symptomatic food allergy to peanut, hazelnut, walnut, cow's milk, hen's egg, and/or soybean allergy. Patients are included to evaluate the effect of dupilumab on change in clinical eliciting dose (ie, lowest dose causing an allergic reaction) [213]. Each patient undergoes 2 oral food challenges: one at screening and the other during treatment with dupilumab (at least 28 weeks).

Allergic Rhinitis

AR is one of the most common comorbidities in patients with uncontrolled, persistent asthma [214]. AR co-occurs in nearly 75%-80% of all patients with asthma and up to 100% of allergic asthma patients [215,216]. Seasonal AR is usually caused by pollens, whereas perennial AR is often associated with sensitization to indoor allergens. Perennial AR is generally considered more challenging to treat than seasonal AR, and symptoms often persist despite best care [217]. Indeed, comorbid AR is a marker of poor control or more severe asthma [218-220].

In a pivotal, phase 2b study (NCT01854047), dupilumab improved key asthma outcomes in the overall population with uncontrolled, persistent asthma and improved AR-associated nasal symptoms in the subgroup of patients with comorbid perennial AR [221]. Weinstein et al [222] evaluated dupilumab treatment in patients with persistent asthma and comorbid perennial AR. Dupilumab decreased AR-associated nasal symptoms significantly, specifically by reducing the 22-item Sino-Nasal Outcome Test (SNOT-22) total score and its AR-associated items in asthma patients with comorbid perennial AR [222]. Dupilumab 200 mg every 2 weeks demonstrated numerically—but not statistically—significant decreases in the total SNOT-22 score.

A post hoc analysis of the phase 3 LIBERTY ASTHMA QUEST study evaluated the effects of dupilumab in the subgroup of patients with comorbid perennial AR [223]. A total of 814 of the 1902 patients (42.8%) had comorbid perennial AR. Dupilumab 200 and 300 mg every 2 weeks reduced severe exacerbations rates and improved FEV_1 compared with placebo; greater efficacy was observed in patients with elevated baseline blood eosinophil counts (≥300 cells/μL) and FeNO. Dupilumab treatment also numerically improved the 5-item Asthma Control Questionnaire and Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) +12 score. By week 52, compared with placebo, treatment with 200 mg or 300 mg of dupilumab every 2 weeks had improved RQLQ+12 subscore in 6 of 7 domains (activities, sleep, practical problems, nasal symptoms, eye symptoms, and emotions; $P<.05$ for all) [223].

In a multicenter, prospective, observational, real-life study in 16 Italian care centers, Nettis et al [224] evaluated the benefit of dupilumab after 16 weeks of treatment in perennial AR and perennial allergic asthma caused by indoor allergens in adults with severe AD. In patients with comorbid perennial AR (n=41), dupilumab was associated with significant improvements in disease control (measured using the Rhinitis Control Scoring System) and in perennial AR quality of life (measured using the RQLQ) [224].

Regarding seasonal AR, a recently completed study evaluated the efficacy of dupilumab as an adjunct to subcutaneous grass immunotherapy to reduce provoked AR symptoms, as measured using the Total Nasal Symptom Score after nasal allergen challenge with timothy grass extract at week 17 (NCT03558997) [225]. The study included 103 patients at 17 study sites in the United States and Canada. Participants who met the eligibility criteria were randomized at a 1:1:1:1 ratio to 1 of 4 treatment groups: placebo, dupilumab, subcutaneous immunotherapy, and dupilumab + subcutaneous immunotherapy.

An ongoing study is evaluating the efficacy of dupilumab as an adjunct to allergen immunotherapy. This study is a double-blind placebo-controlled trial in adults with moderate-to-severe seasonal AR and allergic sensitization to grass pollen (NCT04502966) [226]. The primary objective is to assess whether the combination of grass allergen sublingual immunotherapy and dupilumab for 2 years is more effective than double placebo in suppressing the nasal allergen challenge response to grass pollen at 1 year after completion of the study medication.

Concluding Remarks

Recent advances in our understanding of T2 inflammation have increased the number of diseases in which T2 inflammation is suspected. Dupilumab is a recently developed monoclonal antibody that blocks signalling of the cytokines IL-4 and IL-13, both of which play a key role in T2 responses. As was the case with omalizumab, possible new indications are increasingly explored and include cutaneous, respiratory, and gastrointestinal disorders. Data for most of these conditions are from case reports or small series, although for others, phase 2 and 3 studies are ongoing. It is unknown whether new indications will appear for dupilumab. However, for some diseases, for example, EoE, the possibility seems to be high. In any case, there is no doubt that we are entering a fascinating new era in the management of T2 disorders.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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