Invited Review Article

Dupilumab: Basic aspects and applications to allergic diseases

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A R T I C L E  I N F O

Article history:
Received 18 November 2019
Available online 30 January 2020

Keywords:
Asthma
Atopic dermatitis
Chronic rhinosinusitis with nasal polyps
Interleukin-4
Interleukin-13

A B S T R A C T

Interleukin (IL)-4 and IL-13, signature type 2 cytokines, exert their actions by binding to two types of receptors sharing the IL-4R α chain (IL-4Rα). Since IL-4 and IL-13 play important and redundant roles in the pathogenesis of allergic diseases, blocking both the IL-4 and IL-13 signals would be a powerful and effective strategy for treating allergic diseases. Dupilumab (Dupixent®) is a fully human monoclonal antibody recognizing IL-4Rα and blocking both the IL-4 and IL-13 signals. Dupilumab was first prescribed for atopic dermatitis (AD) patients and has been widely approved for adult patients with moderate to severe AD since 2018. Dupilumab has since been used for asthma, receiving approval for uncontrolled asthma in 2019. A phase 3 study using dupilumab for chronic rhinosinusitis with nasal polyps (CRSwNP) has been just completed, with positive results. Several clinical trials of dupilumab for other diseases in which type 2 inflammation is dominant are now underway. It is hoped that dupilumab will open the door to a new era for treating allergic patients with AD, asthma, and CRSwNP, and for more patients with type 2 inflammations.

Introduction

Interleukin (IL)-4 and IL-13 are signature type 2 cytokines, both exerting their actions by binding to two types of receptors sharing the IL-4R α chain (IL-4Rα). Since IL-4 and IL-13 are important in the pathogenesis of allergic diseases, several drugs aiming at blocking IL-4 and/or IL-13 signals have been developed. Dupilumab (Dupixent®) is a fully human monoclonal antibody belonging to IgG4, recognizing IL-4Rα and blocking both the IL-4 and IL-13 signals. Dupilumab was commercialized as a drug for atopic dermatitis (AD) in 2018 and for asthma in 2019. A phase 3 trial of dupilumab for chronic rhinosinusitis with nasal polyps (CRSwNP) has been just completed, with positive results. The IL-4 and IL-13 signals are thought to be important for many other diseases, and clinical trials are now underway for allergic contact dermatitis, allergic rhinitis, aspirin-exacerbation respiratory disease, alopecia, cholinergic spontaneous urticaria, chronic hand eczema, COPD with type 2 inflammation, eosinophilic esophagitis/gastroenteritis, peanut allergy, and prostate cancer (https://clinicaltrials.gov/ct2/home). In this review article, we focus on the basic aspects of dupilumab and on its clinical applications to AD, asthma, and chronic rhinosinusitis.

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Peer review under responsibility of Japanese Society of Allergology.

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https://doi.org/10.1016/j.alit.2020.01.002
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Basic aspects of dupilumab

Production of IL-4 and IL-13

IL-4 and IL-13 are signature type 2 cytokines. Th2 cells have been thought to mainly produce both IL-4 and IL-13. It has recently been revealed that group 2 innate lymphoid cells (ILC2) are important sources of IL-13, whereas follicular helper T cells (Tfh) are, along with Th2 cells, sources of IL-4. Additionally, mast cells, basophils, and eosinophils also secrete IL-4 and IL-13. Expression of IL-4 and IL-13 is significantly enhanced in the inflamed sites of allergic diseases such as AD, asthma, and chronic rhinosinusitis in which type 2 inflammation is dominant.

Composition of IL-4 and IL-13 receptors

Both IL-4 and IL-13 bind to their receptors on their target cells. Two forms of IL-4Rs exist: type 1 IL-4R and type 2 IL-4R (Fig. 1). Type 1 IL-4R is composed of IL-4Rα and the common γ chain (γc) that is shared by IL-2, IL-7, IL-9, IL-15, and IL-21, whereas type 2 IL-4R comprises IL-4Rα and the IL-13Rα1 chain (IL-13Rα1). Because IL-13 also binds to type 2 IL-4R, this receptor acts as the functional IL-13R. Hematopoietic/immune cells mainly express type 1 IL-4R, whereas type 2 IL-4R/IL-13R is ubiquitously expressed on non-hematopoietic/immune cells or tissue-resident cells. Due to the different distributions of IL-4R/IL-13R and the concentrations of IL-4/IL-13, IL-4 exerts its actions mainly in hematopoietic/immune cells, whereas IL-13 does so mainly in non-hematopoietic/immune cells. Another IL-13 binding component that exists, in addition to IL-13Rα1, is the IL-13Rα2 chain (IL-13Rα2), which cannot transduce signals that act as a decoy receptor. However, the role of IL-13Rα2 in the IL-13 signals is controversial; there are several reports showing that the cytoplasmic tail of IL-13Rα2 interacts with some signal-transducing molecules involved in the IL-13 signals.

Signal pathways of IL-4 and IL-13

The JAK/STAT pathways are the main signal pathways for IL-4 and IL-13 as well as for other cytokines. Addition to these pathways, MAP kinase and phosphatidylinositol-3 kinase pathway are also involved. IL-4Rζ, γc, and IL-13Rα1 bind to JAK1, JAK3, and TYK2, respectively, activating STAT6, along with STAT1 and STAT3 in some cases, and play a critical role in the IL-4/IL-13 signals (Fig. 1).

IL-4 is an essential factor for type 2 inflammation because it induces Th2 differentiation in T cells and class switching into IgE in B cells. Although IL-13 also has the potency to induce class switching into IgE, its ability is less than that of IL-4. Additionally, IL-4 and IL-13 activate other hematopoietic/immune cells such as mast cells, basophils, and macrophages. IL-13, and to a lesser extent IL-4, act on non-immune/hematopoietic cells such as epithelial cells, fibroblasts, and smooth muscle cells. In airways, IL-13 causes goblet cell hyperplasia in epithelial cells and proliferation of smooth muscle cells. IL-13, and to a lesser extent IL-4, induce deposition of extracellular matrix (ECM) proteins in fibroblasts and production of inflammatory mediators such as cytokines and chemokines in various cells. Together, the actions of IL-4 and IL-13 on both hematopoietic/immune cells and non-hematopoietic/immune cells are critical in leading to the phenotypes of allergic diseases such as AD, asthma, and CRSwNP.
diminished, suggesting that IL-4 and IL-13 are redundant in inducing asthmatic phenotypes. However, a specific blockage or defect of IL-13 diminishes asthmatic phenotypes more than that of IL-4, demonstrating that IL-13 rather than IL-4 is central in the pathogenesis of asthma in mice.

Analyses of gene-manipulated mice have shown the importance of IL-4 or IL-13 in the pathogenesis of AD as well. Ectopic expression of IL-4 or IL-13 in the skin caused xerosis and pruritic inflammatory skin accompanied by elevated type 2 immune responses, which reproduced all key features of human AD. Moreover, ectopic overexpression of IL-13 in mouse skin showed significant fibrosis, which is typically observed in chronic AD patients. In contrast, although application of IL-4–deficient mice to repeated epicutaneous sensitization to ovalbumin decreased eosinophils and serum IgE, it did not change the thickness of epidermis or dermis, the chemokine expression, or the infiltration of CD45+, CD4+, and CD8+ cells, suggesting again the redundant roles of IL-4 and IL-13 in the pathogenesis of AD in mice.

Application of dupilumab to AD

Background of AD

AD is a common relapsing inflammatory skin disease, frequently associated with perturbed epidermal barrier function and type 2 immune responses to food and environmental allergens. Approximately 20% of adult patients with AD have moderate-to-severe disease until their 30s. AD causes many disease burdens such as poor quality of life (QOL), as assessed by both generic and specific QOL questionnaires. Pruritus and skin pain, repeated flares, mood and sleep disturbances, and co-morbid economic burdens were frequently experienced in this condition, worsening patients’ QOL and impairing their productivity and activity. First-line treatments include topical corticosteroids (TCS) and calcineurin inhibitors (TCI). Systemic immunosuppressants may be prescribed for patients who cannot achieve remission with TCS or TCI. However, according to the study by Simpson et al., adults with moderate-to-severe AD reported problems with itch frequency (85% of patients), duration (41.5% reported itching ≥18 h/d), and severity (6.5 of 10 on a numeric rating scale), moreover, 55% reported AD-related sleep disturbances 5 day/week or more, despite almost half of the patients using systemic therapies in addition to topical anti-inflammatory agents. These findings suggest that many AD patients, especially those with moderate-to-severe disease, are unlikely to be satisfied with current treatments.

Pathogenesis of AD

Perturbed epidermal barrier function, allergic inflammation, and pruritus contribute to the pathogenesis of AD. Intercellular lipids such as ceramides and natural moisturizing factors whose major source is filaggrin are important in maintaining skin barrier function. Decreased levels of ceramides and filaggrin have been reported in patients with AD. Impaired epidermal barrier function in AD patients leads to hypersusceptibility to external stimuli such as saliva and sweat, resulting in non-specific skin inflammation. Allergens such as mites and pollen penetrating barrier-impaired epidermis induce epicutaneous sensitization and type 2 immune reaction, contributing to the “allergic inflammation” in AD. Pruritus is the most bothersome symptom for AD patients. Nowadays, many mediators of pruritus — including type 2 cytokines such as IL-4, IL-13, and IL-31 — have been described. In addition, sensory nerve fibers have been shown to be distributed in the epidermis and cornified layers of AD patients and may play a role in the hypersensitivity to pruritus frequently seen in these patients. Scratching the skin aggravates eczema in AD. Taken together, type 2 cytokines such as IL-4 and IL-13 play major roles in the pathogenesis of AD and are considered to be promising treatment targets.

Fig. 2. The actions of IL-4 and IL-13 on various hematopoietic/immune and non-hematopoietic/immune cells. Diverse actions of IL-4/IL-13 on various hematopoietic/immune and non-hematopoietic/immune cells are depicted.
Clinical study of dupilumab in AD patients

The efficacy and safety of dupilumab for AD have been examined in several global clinical studies. SOLO 1 and SOLO 2 were randomized, double-blind, placebo-controlled, phase 3 trials in adult patients with moderate-to-severe AD who were not adequately controlled with TCS and/or TCI. In these studies, dupilumab was evaluated as a monotherapy in 16-week trials. The primary end points were the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator’s Global Assessment (IGA) and a reduction of two points or more in that score from baseline at week 16. In the participants with moderate (IGA 3) to severe (IGA 4) AD, 36% and 38% of patients who received dupilumab every other week (Q2W) in SOLO 1 and SOLO 2, respectively, and 37% and 36% who received dupilumab weekly (QW) achieved primary outcome, as compared with 10% and 8% who received placebo. In addition, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index (EASI) was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo. The least-squares mean (±SE) percent change in the EASI score from baseline to week 16 was significantly greater among patients receiving dupilumab than among those receiving placebo, with reductions of 72.3 ± 2.6 among those receiving dupilumab Q2W and 72.0 ± 2.6 among those receiving QW dupilumab, as compared with a reduction of 37.6 ± 3.3 among those receiving placebo in SOLO 1. As for pruritus, an improvement of at least four points in the peak score on the pruritus numerical rating scale occurred at week 16 in significantly more patients receiving dupilumab than in those receiving placebo. In these trials, dupilumab significantly reduced patient-reported symptoms of AD assessed with the Patient-Oriented Eczema Measure (POEM) and its effect on sleep, symptoms of anxiety or depression assessed with the Hospital Anxiety and Depression Scale (HADS-A and HADS-S, respectively), and quality of life using the Dermatology Life Quality Index (DLQI). The overall incidence of adverse events was similar in the dupilumab groups and the placebo groups in the two trials. Serious adverse events and adverse events leading to treatment discontinuation were uncommon. Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups. In SOLO 1 and SOLO 2, 8% and 14%, respectively, of patients who received dupilumab Q2W and 19% and 13% who received dupilumab QW reported injection-site reactions, as compared with 6% and 6% who received placebo. Regarding allergic conjunctivitis, 5% and 1% of patients who received dupilumab Q2W and 3% and 1% who received dupilumab QW reported it, as compared with 1% and 1% who received placebo.

CHRONOS was a one-year, randomized, double-blind, placebo-controlled, phase 3 study in adults with moderate-to-severe AD who showed inadequate response to TCS. All participants used concomitant TCS and/or TCI. Co-primary endpoints, at week 16, were patients (%) achieving IGA 0/1 and 2-point or higher improvement from baseline, and EASI-75. At week 16, more patients who received dupilumab plus TCS achieved the IGA 0/1 (39%) who received dupilumab plus TCS QW and 39% who received dupilumab Q2W plus TCS vs 12% who received placebo plus TCS; p < 0.0001) and EASI-75 (64% and 69% vs 23%; p < 0.0001). Week 52 results were similar. As for the safety profile, adverse events were reported in 83% of the patients who received dupilumab QW plus TCS, 88% who received dupilumab alone Q2W, and 266 (84%) patients who received placebo, respectively. According to this ongoing, multicenter, open-label extension study, 130 patients who received continuous dupilumab treatment demonstrated favorable and stable safety and efficacy after 76 weeks.

Regarding conjunctivitis, Akinlade et al. estimated conjunctivitis in randomized placebo-controlled trials of dupilumab in AD (n = 2629), asthma (n = 2876), chronic rhinosinusitis with nasal polyps (n = 60), and eosinophilic esophagitis (n = 47). They reported that conjunctivitis was more frequent with dupilumab treatment in most AD trials, which was mostly mild-to-moderate AD. In dupilumab trials in other type 2 diseases, incidence of conjunctivitis was overall very low, and was similar for dupilumab and placebo. In AD, the incidence of conjunctivitis was associated with AD severity and prior history of conjunctivitis. The pathogenesis of dupilumab-associated conjunctivitis seen in AD patients remains so far unclear.

Real-world experience with dupilumab for AD

In Japan, dupilumab has been approved since April 2018 for adult patients with moderate-to-severe AD. Actually, many patients whose eczema was inadequately controlled with TCS and/or TCI have achieved remission with dupilumab. It is impressive that a substantial number of patients receiving dupilumab have experienced rapid relief from pruritus. A sub-analysis of the results of two phase 3 trials of dupilumab monotherapy (SOLO 1 and SOLO 2) and with concomitant TCS (CHRONOS and CAFE) reveals that atopic dermatitis with dupilumab improves equally well across different anatomical regions. However, in our clinical practices, we sometimes encountered patients whose facial eruptions were refractory to dupilumab while their eczema on the trunk and extremities responded well to it. To understand the inadequate response only in facial eruption, further analysis would be required.

Application of dupilumab to asthma

Background of asthma

Asthma is a common chronic inflammatory disease of the airways. Approximately 5–10% of patients with asthma have severe asthma, exhibiting unsatisfactory symptom control despite using high-dose inhaled corticosteroids (ICSs) in addition to a second controller. This remains a major health problem, with remarkable impacts on mortality, morbidity, and healthcare resources. Asthma can be classified into phenotypes based upon clinical or biological characteristics. It is notable that in more than 50% of asthma patients, there is strong evidence of the pathogenic role of type 2 cytokines such as IL-4/IL-5/IL-13 orchestrating the eosinophilic and allergic inflammatory processes. Development and clinical application of therapeutic drugs corresponding to therapeutic target molecules, including IL-4/IL-5/IL-13, is clearly needed.

Pathogenesis of asthma

As described above, IL-4 and IL-13 play important roles in the pathogenesis of asthma. In particular, IL-13 shows dominant effects for it compared with IL-4. IL-13 facilitates airway smooth muscle contraction and proliferation, and goblet cell hyperplasia, increased extracellular matrix secretion by fibroblasts and subepithelial basal membrane thickening, and airway hyperreactivity (AHR), all of which are features of airway remodeling. It is known that IL-13 increases airway mucus production, and we will describe later the details of the crosstalk between the IL-4/IL-13 pathways and airway mucus production. Notably, IL-13 stimulates the expression of inducible nitric oxide synthase in airway...
epithelial cells, leading to high levels of exhaled fraction of nitric oxide (FeNO). Therefore, we expect to be able to use FeNO as a surrogate biomarker of IL-13.

**Clinical study of dupilumab in asthma patients**

Several randomized, placebo-controlled trials (RCTs) have shown favorable safety and robust efficacy of dupilumab in patients with uncontrolled asthma. Based on clinical data from about 2800 adults and adolescents who participated in three pivotal trials from the global LIBERTY ASThma program, including a phase 2b trial and the phase 3 QUEST and VENTURE trials, dupilumab received approval for uncontrolled asthma in the USA, Europe, and Japan as of September 2019.

In a proof-of-concept phase 2a trial, in patients with persistent moderate-to-severe asthma with elevated blood eosinophils (≥300 cells/μL) or sputum eosinophils (≥3%), dupilumab decreased the frequency of asthma exacerbations and improved FEV1 and Asthma Control Questionnaire scores. Following these promising results, a dose-ranging phase 2b trial was performed to evaluate the efficacy and safety of dupilumab in 776 patients with uncontrolled asthma, irrespective of baseline eosinophil count. Dupilumab given every two weeks was well tolerated and showed significant improvements in FEV1 at week 12, reducing annualized severe asthma exacerbations and improving asthma control. While this study established that a two-weekly dosing regimen was optimal, it did not establish the most appropriate dose.

Given the positive phase 2 results, two phase 3 trials were initiated to provide further evidence for dupilumab. Liberty Asthma QUEST was a multinational, multicenter, phase 3 RCT and enrolled 1902 patients, ≥12 years of age with uncontrolled, moderate-to-severe asthma who maintained continuous treatment with ICS. Subjects were enrolled regardless of their baseline profile of type 2 biomarker and were randomized in a 2:2:1:1 ratio to receive 200 or 300 mg dupilumab as subcutaneous injection or matched-volume placebo every 2 weeks for 52 weeks. The co-primary endpoints were the annualized rate of severe asthma exacerbations and the absolute change in pre-bronchodilator FEV1 from baseline to week 12 in the overall trial population. An analysis of the effect of dupilumab on exacerbations and the FEV1 was conducted on the basis of both the baseline FeNO and the baseline blood eosinophil count (Fig. 4, 5). In the intention-to-treat population, the annualized rate of severe asthma exacerbations was significantly reduced, with greater effects observed when increased baseline levels of FeNO or blood eosinophils were present. Dupilumab improved the FEV1 and the effect was significant in patients whose baseline FeNO ≥25 ppb and in those with a baseline blood eosinophil count of ≥300 cells/μL. The improvement in FEV1 began two weeks after initiating treatment and was subsequently maintained for the 52-week treatment period. Higher baseline FeNO levels were also predictive of greater response to dupilumab in terms of both exacerbations and the FEV1 findings that suggest the importance of other type 2 biomarkers beyond blood eosinophils. Moreover, a prespecified analysis of the rate of change in the post bronchodilator FEV1 showed a loss of lung function of 40 mL/year with placebo and no loss with either dupilumab dose. This finding could be beneficial in reducing the progression of airflow limitation.

Liberty Asthma VENTURE enrolled 210 patients with severe oral corticosteroid (OCS) dependent (≥5 mg prednisone or equivalent) asthma and assessed whether adding dupilumab to standard-of-care therapy could reduce the use of maintenance OCS. The OCS dose was reduced every 4 weeks between weeks 4 and 20, as long as asthma control was maintained. Patients treated with dupilumab had significant reductions in their average daily OCS dose by 70%, vs. 42% with placebo at week 24. More than half of the patients treated with dupilumab (52%) were able to completely eliminate their use of OCS (vs. 29% with placebo). Moreover, the reduction of severe asthma exacerbations was seen in subjects receiving dupilumab together with FEV1 improvements.
In asthma clinical trials, the most consistent adverse event of dupilumab was injection site reaction. Although a small number of patients developed peripheral blood eosinophilia, the majority remained asymptomatic, and the eosinophilia did not persist over time. The long-term safety and tolerability of dupilumab remain to be evaluated.

Several studies have recently addressed the crosstalk between IL-4/IL-13 pathways and airway mucus production. Duncan et al. quantified airway mucus plugs from asthma patients using multi-detector computed tomography (CT). They found that mucus plugs were detected in 58% of asthmatics, and a subset of mucus plugs persisted over time. Moreover, mucus plug scores were associated with loss of lung function, exacerbations, and increased sputum eosinophils. Based on a series of in vitro studies, these investigators found that oxidants generated by eosinophil peroxidase (EPO) can oxidize cysteine thiol groups to promote mucus plug formation. IL-13 increases thiocyanate (SCN⁻) transfer into the airway lumen and, as a result, SCN⁻ is oxidized by hydrogen peroxide (H₂O₂) to form hypothiocyanous acid (HOSCN), a reaction catalyzed by EPO, which is an eosinophil-derived enzyme that catalyzes reactions of H₂O₂ with bromide, chloride and thiocyanate to generate potent oxidants. HOSCN targets cysteine thiol groups in the secreted mucin polymer to generate covalent disulfide mucin crosslinks. Crosslinked mucins have a high elasticity that decreases their clearance by the mucociliary escalator and results in mucus plug formation.

Svenningsen et al. quantified airway mucus using CT scan and ventilation heterogeneity using magnetic resonance imaging (MRI) ventilation defect percent (VDP) in patients with severe asthma. Mucus plugs were correlated with MRI VDP, and the CT mucus score was associated with evidence of upregulated IL-4/IL-13 pathways that could be identified according to elevated FeNO values and sputum IL-4 levels. More recently, they reported the case of a severe asthmatic who showed significant improvement of airway mucus score and normalization of MRI ventilation heterogeneity and associated clinical and physiological parameters following treatment with dupilumab. These novel findings raise the possibility that inhibition of IL-4/IL-13 signaling pathway by dupilumab could decrease the presence of mucus plugs, thereby improving lung function.

Currently, the available molecular targeted drugs that can be used in asthma are omalizumab (anti-IgE), mepolizumab, and benralizumab (anti-IL-5 pathways), and dupilumab (anti-IL-4/IL-13).
As a characteristic feature of the phenotype in severe asthma in Japan, more than 80% of patients exhibited some sub-phenotype of type 2-high asthma: eosinophilic, FeNO-high/periostin-high, or atopic asthma. With the approval of multiple biologic medications in a short period, the clinical question of how physicians should choose a biologic remains largely unanswered. From the viewpoint of a patient's biomarkers, a high FeNO level of ≥50 ppb can predict a very favorable response to dupilumab, and intermediate FeNO levels of ≥25 ppb may also predict a favorable response, especially in patients with blood eosinophilia (≥300 cells/μL). From the viewpoint of a patient's clinical background, dupilumab may be effective for type 2-high patients with persistent airflow limitation and the presence of mucus plugs, combined with AD and/or nasal polyposis. However, in cases with marked blood eosinophils, considering the risk of elevating blood eosinophil count with dupilumab, anti-IL-5 therapy may be preferable.

In summary, four major RCTs have confirmed dupilumab to be an effective and safe therapy for refractory asthma, particularly in patients with a type 2-high subtype. Further studies are needed to select the appropriate biologic for individual asthma patients.

**Application of dupilumab to CRSwNP**

**Background and pathogenesis of CRSwNP**

Patients with chronic rhinosinusitis (CRS) complain of symptoms such as purulent nasal discharge, nasal obstruction, headache, and dysosmia. CRS arises as the response of the paranasal sinuses to viral infection and secondary bacterial infection, followed by persistent inflammation. In Japan, CRSwNP was primarily a neutrophilic disease until the late 1990s, and endoscopic sinus surgery (ESS) combined with postoperative macrolide therapy was effective for neutrophilic CRSwNP. However, an increasing number of CRSwNP patients complain of loss of smell and have a viscous nasal discharge. This type of CRSwNP recurs soon after ESS with postoperative macrolide therapy and is associated with eosinophil-dominant inflammatory cell infiltration, instead of the previously common neutrophil-dominant infiltration. Such intractable CRSwNP has been termed eosinophilic CRS (ECRS).

In Europe, CRSwNP is a predominantly type 2 inflammatory disease associated with a high symptom burden and poor health-related quality of life. ECRS is also predominantly associated with a type 2 inflammatory response. Staphylococcal enterotoxin (SE)-specific IgE is involved in the pathogenesis of CRSwNP. Dendritic cells in the nasal mucosa phagocytose SE, derived from Staphylococcus aureus, transmit information to naive CD4-positive T cells, which differentiate into Th2 cells under stimulation by IL-4 to produce IL-4, IL-5, and IL-13 (Fig. 6). It has been reported that IL-4 promotes the differentiation of B cells into SE-specific IgE-producing plasma cells. At the same time, production of polyclonal IgE in the nasal mucosa is induced by staphylococcal enterotoxin B (SEB) as a superantigen. Binding of IgE to mast cells leads to release of chemical mediators (especially IL-5), resulting in eosinophilic inflammation. Several bacterial proteases, viruses, and various antigens stimulate the production of TSLP and IL-33 by nasal epithelial cells. In turn, TSLP and IL-33 promote the production of type 2 cytokines (IL-4, IL-5, and IL-13) by ILC2 cells in the nasal mucosa, after which IL-4 and IL-13 stimulate secretion by goblet cells in the nasal mucosa. IL-4 induces production of eosinophil chemotactic factors (e.g., eotaxins) by nasal epithelial cells and fibroblasts in response to viral infection, IL-1, and/or TNFα. Stimulation by a combination of IL-4-double-stranded RNA/protease inhibitor CST1 significantly elevates TSLP mRNA and protein levels in nasal epithelial cells. In CRSwNP, coagulation is upregulated and fibrinolysis is downregulated in the nasal mucosa. Tissue plasminogen activator (t-PA) is a key factor in the fibrinolytic cascade. Expression of t-PA is decreased in the nasal mucosa of CRSwNP patients compared with normal nasal mucosa. It was
reported that IL-4/IL-13 decrease t-PA expression in nasal epithelial cells. Also, IL-4 induces the expression of adhesion molecules by endothelial cells that facilitate migration of eosinophils. Thus, IL-4 and IL-13 are major cytokines involved in the pathogenesis of CRSwNP.

Clinical study of dupilumab in CRSwNP patients

Recently, a large phase 3 study was published that assessed the efficacy and safety of dupilumab in patients with severe CRSwNP and previous treatment with systemic corticosteroids, surgery, or both. This study was performed in two parts, which were LIBERTY NP (n = 276, active vs. placebo) and LIBERTY NP SINUS-52 (n = 448, two active vs. placebo arms). SINUS-24 was performed in 13 countries and SINUS-52 involved 14 countries. SINUS-52 included 49 Japanese patients with CRSwNP that was consistent with ECRS. Eligible patients had bilateral nasal polyps and symptoms of CRS. The nasal polyp score was at least 5 (maximum 8), with a minimum score of 2 per nostril. In addition, patients had received systemic corticosteroids in the preceding two years or had undergone ESS.

Dupilumab significantly improved the nasal polyp score (NPS) and the nasal congestion or obstruction score (co-primary endpoints). At 24 weeks, the least squares mean difference of the NPS for dupilumab treatment versus placebo was −2.06 (p < 0.0001) in SINUS-24 and −1.80 (p < 0.0001) in SINUS-52 (Fig. 7). In addition, the difference of the nasal congestion or obstruction score was −0.89 (p < 0.0001) in SINUS-24 and −0.87 (p < 0.0001) in SINUS-52, and the difference of the Lund–Mackay CT score was −7.44 (p < 0.0001) and −5.13 (p < 0.0001), respectively. Common adverse events were nasopharyngitis, exacerbation of nasal polyps and asthma, headache, epistaxis, and injection site erythema. Dupilumab was generally well tolerated. Many CRSwNP patients have comorbidities of allergic diseases and about 60% of the patients had asthma and 28% had nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease.

Systemic corticosteroids and surgery (ESS) are effective for CRSwNP, a type 2 inflammatory disease. However, long-term administration of oral corticosteroids can lead to serious adverse events. Thus, novel therapies to improve disease control are needed to avoid ongoing use of systemic corticosteroids and repeated ESS. The data described above support the benefits of dupilumab as an option for the treatment intractable/refractory CRSwNP (or severe ECRS). Administration of dupilumab led to substantial reduction in the need for systemic corticosteroids and repeat ESS.

Conclusion

Dupilumab has already been approved as a new molecularly targeted drug for AD and asthma and is expected to be approved soon for CRSwNP as well, based on the positive results of the phase 3 study. These results would suggest that the IL-4/IL-13 signals are critical for allergic inflammation beyond the inflamed sites. It is hoped that dupilumab will be effective for other, related diseases involving type 2 inflammation. The diversity of response to dupilumab in AD and CRSwNP patients has not yet been examined, whereas FeNO and blood eosinophils are thus far useful biomarkers for predicting the efficacy of dupilumab in asthma. It is hoped that stratification of allergic patients in relation to the efficacy of dupilumab will make it possible to develop precision medicine for allergic diseases.

Acknowledgements

We thank Dr. Dovie R. Wylie for critical review of this manuscript.

Conflict of interest

KM received speaker fees from AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi. NK received honoraria for lectures and research grants from Sanofi (France, Research funding-2019-207) and Regeneron (USA, R3500-AD-1805). SF has been an advisory board member for GlaxoSmithKline, Kyowa Kirin, and Sanofi and received speaker fees from Kyorin, Taiho, and Mitsubishi Tanabe Pharma. KI received research grants from Sanofi. The rest of the authors have no conflict of interest.

References


