Dupilumab: New Opportunities for the Treatment of Asthma and Chronic Rhinosinusitis with Nasal Polyps

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ABSTRACT
Airway inflammation plays a crucial role in the development of asthma and chronic rhinosinusitis with nasal polyps (CRSwNP). The severity of inflammation influences the clinical picture of the disease and, most importantly, the effectiveness of therapy.

To date, the growth in the incidence rate of asthma and CRSwNP is still high and the effectiveness of existing therapy for severe asthma, especially associated with CRSwNP, is unsatisfactory. Therefore, the aim is to investigate novel diagnostic tools and therapies.

The emergence of biologics that target specific inflammatory pathways is a promising step forward to achieve control of severe uncontrolled asthma and recurrent CRSwNP. Dupilumab is one of recently introduced monoclonal antibodies, which has shown significant advances in the treatment of asthma and CRSwNP.

Dupilumab is a fully human monoclonal antibody targeted to interleukin-4 receptor alpha subunit (IL-4Rα) that is a receptor for both IL-4 and IL-13. Thus, it helps to inhibit cytokine T2-signaling (IL-4 and IL-13), since the IL-4/IL-13/STAT6 signaling pathway plays a crucial role in T2-inflammation.

In Russia, dupilumab is currently approved as a treatment for atopic dermatitis (in children over 6 years of age), asthma (in children over 12 years of age) and severe CRSwNP in adults. This article summarizes the main data on dupilumab and its efficacy in patients with asthma and CRSwNP and presents a relevant case report.

Keywords: IL-4; IL-13; asthma; chronic rhinosinusitis with nasal polyps; dupilumab; biological therapy

Introduction

The studies of the early century aimed to investigate the pathophysiology of asthma and provided data indicating complex mechanisms of its development [1,2]. This helped to classify asthma not only by phenotypes, but also by endotypes that included T2-asthma and non-T2-asthma. The endotypes were characterized by different risk factors and mechanisms of inflammation, thus influencing the therapy of asthma [3,4].

T2-inflammation is associated with the generation of abundant quantities of interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) [5]. These cytokines play an important role in the pathogenesis of asthma. IL-5 promotes the differentiation, maturation, and survival of eosinophils, while IL-4 and IL-13 are involved in the differentiation of Th2 lymphocytes and the recruitment of eosinophils into airways (where they contribute to epithelial damage). Moreover, IL-4 and IL-13 stimulate goblet cells to secrete mucus and epithelial cells to produce nitric oxide. They also induce the synthesis of immunoglobulin E (IgE) [6,7].

Numerous concomitant diseases that affect the inflammatory mechanisms and the course of asthma have been described, including chronic rhinosinusitis with nasal polyps (CRSwNP). Chronic rhinosinusitis with nasal polyps should be considered a risk factor for uncontrolled severe asthma. Since upper airway inflammation prompts lower airway inflammation and vice versa [8,9,10], the exacerbations of asthma in such patients are more frequent and require admission to hospital in order to manage the episode. Moreover, the treatment requires a longer time [10].

According to epidemiological studies, the prevalence of asthma in patients with CRSwNP is significantly higher (45–76%) [11]. It is primarily due to the close anatomical relationship of the upper and lower respiratory tract, similar mechanisms of inflammatory response, and complex nasobronchial interactions under nervous system control. The cause of CRSwNP is still unknown and it cannot be treated completely due to frequent relapses.

It should be noted that signs of polyp tissue and bronchial mucosa remodeling in asthma patients have common features such as increased collagen production, thickening of the basement membrane, hypertrophy and hyperplasia of the submucous glands, and epithelial metaplasia [12,13]. At the same time, in most cases, the pathogenesis of CRSwNP is also characterized by T2-inflammation, with IL-5 promoting the eosinophil recruitment in the upper airways and IL-4 stimulating B cells, which activate mast cells and basophils, to produce IgE. At the following stage, macrophages stimulated by IL-13 start to produce factor XIIIa (fibrin stabilizing factor), which is involved in the formation of cross-sectional fibrils in the nasal mucosa during polyp development [14].

Thus, the development of asthma and CRSwNP is associated with similar biotargets involved in the inflammatory process. Therefore, the development of biologics for asthma should be focused on therapies directed towards IL-4, IL-5, and IL-13. Also, the relationships between asthma and CRSwNP should be considered. Overall, the introduction of dupilumab that targets the signaling of IL-4 and IL-13 has become a breakthrough in the development of monoclonal antibodies.

Dupilumab as an anti-IL-4 and anti-IL-13 biologic

IL-4 and IL-13 are significant contributors to T2-inflammation since they activate numerous types of cells (T and B cells, mast cells, eosinophils, NKT cells, macrophages, etc.) and induce the production of IgE, histamine, eicosanoids, leukotrienes, chemokines, cytokines, and TARC (thymus and activation regulated chemokine) [15,16] (see Fig. 1).

The inhibition of IL-4/IL-13 signaling pathway in patients with asthma and CRSwNP leads to a decrease in T2-inflammation biomarkers, including IgE, periostin, and numerous pro-inflammatory cytokines and chemokines (e.g. eotaxin, TARC), and reduces the level of fraction of exhaled nitric oxide (FeNO), which is a lung inflammation biomarker [17].

In most cases, IL-4 and IL-13 are produced by CD4+ Th2 cells, with ILC2 cells producing mainly IL-13. These cytokines are also secreted by mast cells,
IL-4 and IL-13 play a key role in the development of asthma and CRSwNP since they provide a variety of inflammatory and structural changes associated with these respiratory diseases.

Numerous studies evaluating the efficacy and safety of several drugs targeting IL-13 (lebrikizumab, tralokinumab) have been carried out worldwide, but the endpoints were not achieved in phase III studies [24-26]. Also, the mechanisms of action of pascolizumab (anti-IL-4 antibody) [27], humanized anti-IL-4 monoclonal antibodies, and pitrakinra (the recombinant interleukin-4, which binds to IL-4Rα and thereby inhibits IL-4 and IL-13 signaling), have been studied [28,29]. However, these substances, except for dupilumab, were not allowed to...
be investigated in subsequent studies. In contrast, dupilumab has passed all phases of clinical trials proving its safety and efficacy.

The mechanism of action of dupilumab significantly differs from that of the majority of monoclonal antibodies (see Fig. 2) used in clinical practice for the treatment of asthma, since they mostly target IL-5 (mepolizumab and reslizumab), IL-5Rα (benralizumab), and IgE (omalizumab). Dupilumab binds to the IL-4Rα specifically and with high affinity. IL-4 signaling is mediated by the type I receptor, which includes the IL-4 receptor subunit alpha and the common γ-chain (IL-4α/γc). IL-4 and IL-13 signaling may also occur via the type II receptor, which includes the IL-4 receptor subunit alpha and IL-13 receptor subunit alpha one (IL-4α/IL-13Rα1) [30-32]. Therefore, dupilumab inhibits both type I and type II receptor signaling.

In the Phase 2b and Phase 3 clinical trials [33] in adults and adolescents with moderate and severe asthma, subcutaneous injections of dupilumab at doses of 200 mg and 300 mg for up to 52 weeks helped to reduce the exhaled nitric oxide [34,35], total serum IgE, TARC, eotaxin-3 and/or periostin levels [36] compared to placebo (p <0.001).

The studies showed an almost maximum decrease in these biomarkers after two weeks of dupilumab therapy [34,35,36] (except for IgE, which showed a less prominent decrease) that was largely maintained throughout the treatment [30,31,35,36].

Also, dupilumab reduced pulmonary eosinophilic infiltration, goblet cell metaplasia, and lung dysfunction in murine model of allergen-induced type 2 inflammation. Some patients who received dupilumab developed anti-drug antibodies that were usually characterized by low titers and did not affect the exposure, efficacy, or safety of the drug [30,31,33,34].

Thus, dupilumab is a promising biologic in the treatment of asthma and CRSwNP, since these diseases are characterized by the prevalence of T2-inflammation and IL-4 and IL-13 as dominating cytokines.

The role of dupilumab in the treatment of asthma and chronic rhinosinusitis with nasal polyps

Phenotyping and endotyping of asthma is crucial for diagnosis and treatment, since it provides a more targeted approach. In this regard, various multi-center, placebo-controlled clinical trials aimed to investigate the efficacy of monoclonal antibodies for asthma, taking into account its phenotypes and endotypes, are being conducted all over the world.

To date, dupilumab has been studied in at least 3000 patients with asthma, atopic dermatitis, CRSwNP, and eosinophilic esophagitis and has shown an acceptable safety profile in placebo-controlled trials that were conducted in Russia.

Three important double-blind, placebo-controlled studies with randomized treatment periods of 24–52 weeks have been conducted worldwide. They evaluated...
the efficacy of subcutaneous dupilumab injections in addition to standard therapy of adults and adolescents with moderate or severe asthma [14,37,38]. These Phase 3 (QUEST [14] and VENTURE [37]) and Phase 2b (DRI12544 [38]) studies from the LIBERTY clinical trial program included patients aged ≥12 or ≥18 years with asthma persistent for 12 months or more. The inclusion criteria for the studies did not determine minimum eosinophil counts or other T2-biomarker levels, but patients with absolute eosinophil counts over 1500 cells/μL were not included [39].

QUEST and DRI12544 studies were primarily designed to assess severe asthma exacerbations and pulmonary function [14,38]. VENTURE study [37] assessed the possibility to reduce glucocorticoid (GC) dose or to withdraw GC, the symptoms of asthma being controlled. Therefore, the patients should have been treated with systemic GC and high doses of inhaled GC (IGC) for 6 months and 3 months before participation, respectively. Prior to randomization, the participants had been reducing their GC dose for 3–10 weeks to the minimum dose at which symptoms could be controlled. This period was followed by randomization and a 24-week treatment period, which included the induction phase (0–4 weeks), during which patients received their optimal dose of GC, a GC reduction phase (4–20 weeks), when the GC dose was decreased every 4 weeks under control of asthma, and a maintenance phase (20–24 weeks), in which the GC dose that was set at the end of phase 2 remained unchanged.

In all the studies described, the mean age of patients was about 50 years, the FEV1 was 52–61%, and the mean eosinophil count was about 347-360 cells/μL. The study showed that the addition of dupilumab to the existing therapy led to a decrease in severe exacerbations of asthma in adults and adolescents with asthma that was not previously controlled with medium and high doses of inhaled [14,38] or systemic GC [37].

M. Castro and C. Rabe, who were the leading investigators in the studies [14,38], noted that a more pronounced decrease in the frequency of asthma exacerbations in patients with glucocorticoid-independent asthma was associated with FeNO ≥25 ppb and eosinophil counts ≥150/μL (the relative risk of exacerbations reduced by 65–68% versus placebo) [15]. At the same time, the subgroup with higher FeNO levels (≥50 ppb) showed a more significant reduction in the exacerbation risk (69–70% compared to placebo). Similarly, the subgroup with high baseline eosinophil level (≥300 cells/μL) demonstrated a 66–67% reduction in exacerbation risk compared to placebo. Spirometry data showed that in group with eosinophil counts ≤150 cells/μL and FeNO <25 ppb the mean difference in FEV1 before dupilumab-induced bronchodilation was not significant (<100 ml) compared to the placebo group. In addition, the increase in the biomarker activity led to a significant increase in the efficacy of dupilumab assessed by FEV1 levels. The subgroups of patients with the baseline eosinophil level of ≥300 cells/μL demonstrated an absolute increase in FEV1 of more than 450 ml compared to the baseline.

In VENTURE study [37], dupilumab showed a higher probability of daily GC dose reduction to a level of <5 mg compared with placebo (statistically significant difference from the placebo group was shown regardless of the baseline eosinophil level). Forty-eight percent (48%) of patients from the treatment group discontinued GC therapy (regardless of the baseline eosinophil level, p =0.002).

The treatment with dupilumab was associated with increased eosinophil levels (mainly transient) in 4–13% of patients. However, it was accompanied by a positive clinical effect on severe asthma [40,41]. This may be due to the fact that dupilumab blocks eosinophil migration by inhibiting the production of eotaxins mediated by IL-4 and IL-13 (confirmed by the decrease in eotaxin-3 blood level [14]) and vascular cell adhesion molecules [42,43]. The patient’s leaflet for Dupixent® indicates that some patients participating in the clinical trial, which assessed the drug for asthma, and some adult patients with concomitant asthma participating in the study, which assessed the drug for CRSwNP, developed eosinophilic pneumonia and vasculitis, corresponding to eosinophilic granulomatosis with polyangiitis. The relation between Dupixent® treatment and these events was not observed. The incidence rate of treatment-related eosinophilia (≥500 cells/μl) was similar in Dupixent® and placebo groups. Less than 2% of patients from the Dupixent® group and less than 0.5% of patients from the placebo group developed treatment-related eosinophilia (>5000 cells/μl).

The studies revealed that patients with baseline eosinophil counts of at least 300 cells/μL had an increase after the initiation of treatment, but it did not affect the effectiveness of therapy. Thus, it is necessary to investigate the effect of dupilumab on eosinophil levels in the peripheral blood, since there is no data indicating a distinct relationship between the dupilumab therapy and eosinophilia. To prescribe biological drugs correctly, the diagnosis is to be verified thoroughly for each patient with severe asthma and blood hypereosinophilia to exclude systemic hypereosinophilia.

The safety and efficacy of dupilumab in asthma patients are of great interest for the use of this monoclonal antibody in CRSwNP patients [44]. Moreover, many patients have both asthma and CRSwNP. In such cases, asthma is more severe, uncontrolled, and with more severe airway obstruction than in asthma patients without CRSwNP. In such cases, CRSwNP becomes recurrent, leading to frequent surgical interventions.

The mucous membranes of the nasal cavity, paranasal sinuses, and lower respiratory tract are interconnected due to anatomical, physiological, and immune characteristics. Therefore, inflammation in the upper and lower airways leads to a decrease in their lumen, an increase in the amount of nasal and bronchial secretions, and hyper-
reactivity. CRSwNP should be considered a risk factor for uncontrolled severe asthma. Patients with asthma are thought to have severe inflammation in the lower airways due to CRSwNP; therefore, such patients often require hospitalization for the treatment of asthma exacerbation that takes a longer time [45,46].

Recent studies have shown that the treatment of CRSwNP in asthma patients improves their condition, reduces the number of visits and the amount of medications. Therefore, it is important to develop a monoclonal antibody (dupilumab), which will be equally efficient and safe in both asthma and CRSwNP patients.

Given the data on the relationships between asthma and CRSwNP, in 2019, Bachert C et al. conducted two large international, multicenter, randomized, double-blind, placebo-controlled studies in parallel groups (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52) [47]. They assessed the effectiveness of dupilumab as an adjunct to standard therapy in adult patients with severe CRSwNP taking into account the data on asthma and CRSwNP interaction. The subjects had comorbidities specific for CRSwNP, i.e. asthma (59%), allergic rhinitis (58%), and aspirin-induced respiratory disease (28%). SINUS-24 study was conducted in 67 sites in 13 countries, while SINUS-52 study was conducted in 117 sites in 14 countries. The patients were randomized (1:1) to subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks and every 2 weeks for the remaining 28 weeks or placebo every 2 weeks for 52 weeks. Nasal endoscopy and paranasal sinus computed tomography revealed that the polyp size decreased significantly, which also had a positive effect on sinonasal symptoms (nasal congestion and rhinorrhea decreased). Almost all patients (97%) received systemic corticosteroids and the regimen of therapy with budesonide/formoterol 160/4.5 μg was changed to 2 inhalations thrice daily. The therapy led to positive effect (nasal congestion decreased).

After developing ketoprofen-induced asthma, the patient started to complain of shortness of breath on exertion, episodes of dyspnea, cough producing light yellow sputum, chest congestion, night awakenings due to choking, nasal congestion, and lack of smell during the last 5 years.

**History of the present illness.** The patient has a history of asthma since 5 years of age and allergy to household agents since 10 years of age. The patient is a non-smoker. Her inhalation therapy included budesonide/formoterol at a dose of 160/4.5 μg (two inhalations twice daily) and montelukast at a dose of 10 mg (one tablet once daily). She suffers from nasal congestion and nasal discharge since 14 years. At the age of 16, she noted the lack of smell and was diagnosed with chronic rhinosinusitis with nasal polyps That was treated with mometasone furoate (50 μg, two doses twice daily). At the age of 17, the patient received the first course of house dust allergen-specific immunotherapy (SIT), followed by two courses. The therapy led to positive effect (nasal congestion decreased).

**Case Report**

A 27-year-old female patient attended to the hospital complaining of shortness of breath on exertion, episodes of dyspnea, cough producing light yellow sputum, chest congestion, night awakenings due to choking, nasal congestion, and lack of smell during the last 5 years.

**Physical examination.** On examination, the patient’s condition was satisfactory. The skin was intact with no abnormalities in color and moisture. Nasal breathing was severely impaired. Auscultation revealed rough breathing sound and nonmusical crackles in the middle and lower lobe areas. The respiratory rate (RR) was 20 breaths/minute and oxygen saturation (SpO2) was 97%. The heart sounds were normal, the heart rate (HR) was 65 bpm, and the blood pressure (BP) was 117/65 mm Hg.
120/80 mm Hg. Abdominal palpation revealed no pain or rigidity.

*Laboratory and instrumental findings.* The eosinophil count was 600 cells/μL. Chest X-ray showed prominent perihilar markings with hilar thickening mostly on the left side. The diaphragm and pleural recesses are visible. The heart and the aorta are normal. Spirometry revealed severe bronchial obstruction (see Table 1).

*Allergy testing.* Skin prick tests to house dust mites allergens were positive.

Histology showed eosinophilic chronic rhinosinusitis with nasal polyps, with the eosinophil/neutrophil ratio being 5.1. The severity of eosinophil infiltration was grade 3 (marked infiltration, over 400 cells per 10 fields of view).

*Clinical Diagnosis.* The patient was diagnosed with partially controlled severe persistent mixed asthma, grade 0 respiratory failure, moderate persistent allergic rhinitis, sensitization to household allergens, chronic rhinosinusitis with nasal polyps, and hypersensitivity to nonsteroidal anti-inflammatory drugs.

Due to the lack of asthma control despite the treatment using high doses of IGCs/long-acting β2-agonists (LABA), long-acting anticholinergic drugs, as well as the presence of recurrent CRSwNP, the patient was prescribed with target dupilumab therapy at a dose of 300 mg subcutaneously every 2 weeks.

*The results of dupilumab therapy.* After 2 weeks of treatment, the patient noticed significant improvement, including the reduction in cough and shortness of breath. Evaluation of the patient’s condition 3, 6, and 12 months after the initiation of therapy revealed an improvement in spirometry parameters (see Table) and asthma control, a further decrease in shortness of breath and episodes of dyspnea, and an increase in tolerance to exercise. It should be noted that peripheral eosinophilia tended to reduce after 6 months of therapy and after 12 months was as low as 380 cells/μL compared to 600 cells/μL at baseline. The data obtained showed that eosinophil count tends to decrease gradually after the initial increase associated with the dupilumab therapy. Therefore, every patient should be thoroughly evaluated to exclude systemic hyperesinophilia prior to initiation of dupilumab therapy.

No asthma exacerbations occurred during 6 months of dupilumab treatment. After 6 months of treatment, the regimen of standard therapy was adjusted. The IGC/LABA (budesonide/formoterol) dose was reduced to 640/18 μg daily. The dose of montelukast and tiotropium bromide remained unchanged.

As for CRSwNP, its course improved since the nasal congestion and the need for topical GCs decreased. After one month of treatment, the patient noted the ability to smell. ENT-examination and paranasal sinus multislice spiral computed tomography (MSCT) showed the regression of polypos (nasal polypectomy was not performed) (see Figure 3). The patient continued dupilumab therapy in the same dosing regimen.

Within this case report, it should be noted that ineffectiveness of previous treatment required the subsequent treatment with systemic GCs that is associated with serious adverse events. Dupilumab therapy helped to improve the course of asthma and CRSwNP and prevent the initiation of systemic GC therapy and, therefore, the development of adverse events. Moreover, according to the published data, sinus polypectomy is associated with a 50% risk of relapse during three years [47]. In this case report, polypectomy was not performed during 12 months of treatment. Moreover, the polyps did not increase in size during this period.

Therefore, the initiation of monoclonal antibody therapy with dupilumab allowed us to control asthma and CRSwNP without the extension of therapy and surgeries, which significantly improved the patient’s quality of life.

**Conclusion**

During the last decade, the biologics have provided the major advance in the treatment of allergic diseases with more effective and safe monoclonal antibodies, with dupilumab being one of them.

Dupilumab therapy has become a breakthrough in treatment of patients with asthma and/or CRSwNP. This therapy showed its favorable safety profile and efficacy in the treatment of T2-inflammatory diseases. Dupilumab is essential for CRSwNP treatment, since it helps to avoid the adverse effects associated with systemic GC therapy and reduce the number of surgical re-interventions.

Today, it is necessary to understand which patients are the best and the worst responders to this therapy. Therefore, further research aimed to identify relevant phenotypes and biomarkers with their subsequent analy-

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Note. FVC — Forced Vital Capacity; FEV₁ — Forced Expiratory Volume in 1 second; PEF — Peak Expiratory Flow; PFM — Peak Flow Meter.
sis in order to predict the efficacy of dupilumab therapy is required.

Thus, biological therapy based on the phenotypes and endotypes of asthma will become a personalized medicine strategy for the treatment of asthma and CRSwNP.

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