DOI: https://doi.org/10.36691/RJA1390

T2 asthma and T2-associated diseases: a consolidated approach to biological therapy

© **N.M. Nenasheva**

Federal State Budgetary Educational Institution of Additional Professional Education Russian Medical Academy of Continuous Professional Education; Moscow, Russian Federation

BACKGROUND: This article is dedicated to the main characteristics of severe bronchial asthma (SBA) and its heterogeneity. In particular, it describes T2 asthma and the role of the main cytokines involved in T2 inflammation. It focuses on the role of IL-4 and IL-13 in the pathogenesis of asthma and other T2-associated diseases, as key cytokines in the initiation and maintenance of T2 inflammation. The article presents the results of experimental studies proving that the activation of IL-4/IL-13 can cause significant hyperresponsiveness of the human airway smooth muscles and the combined blockade of the activity of these cytokines using a human monoclonal antibody against the common IL-4/13 receptor α-subunit-dupilumab-determines the clinical efficacy not only in relation to exacerbations and control of asthma symptoms, but also an improvement of the lung function and a reduction in bronchial hyperresponsiveness. When type 2 helper cells (Th2) interact with antigen-presenting cells, IL-4 and IL-13 are simultaneously released, therefore, blocking IL-4Rα is more effective than blocking each of the ligands separately, which explains the high efficacy of dupilumab not only in T2 asthma, but also other T2-associated diseases: atopic dermatitis and chronic rhinosinusitis with nasal polyps. In addition to asthma and atopic dermatitis, a new indication for dupilumab, chronic rhinosinusitis with nasal polyps, has recently been approved.
CONCLUSION: According to the recommendations of the European Academy of Allergy and Clinical Immunology (EAACI) for the biological therapy of SBA 2020, dupilumab is recommended as an add-on maintenance therapy in adults and children aged 12–17 years old with uncontrolled severe T2 asthma, including asthma with the allergic and eosinophilic phenotype, as well as mixed (when there are signs of both phenotypes) and steroid-dependent asthma. At the same time, dupilumab is well tolerated.

Keywords: T2 asthma, severe asthma, T2-associated diseases, interleukins 4 and 13, biological therapy, dupilumab

For citation: Nenasheva N.M. T2 asthma and T2-associated diseases: a consolidated approach to biological therapy. *Russian Journal of Allergy.* 2020;17(3):34–49. DOI: https://doi.org/10.36691/RJA1390

Т2 астма и Т2-ассоциированные заболевания: единый подход к биологической терапии

© **Н.М. Ненашева**

Российская медицинская академия непрерывного профессионального образования Министерства здравоохранения Российской Федерации; г. Москва, Российская Федерация

Настоящая статья посвящена основным характеристикам тяжелой бронхиальной астмы (ТБА) и ее гетерогенности, в частности охарактеризована Т2 астма и представлена роль основных цитокинов, формирующих Т2-воспаление. Основной акцент сделан на роли интерлейкина (ИЛ)-4 и ИЛ-13 в патогенезе БА и других Т2-ассоциированных заболеваний как ключевых цитокинов в запуске и поддержании Т2-воспаления. Представлены результаты экспериментальных исследований, доказывающих, что активация ИЛ-4/ИЛ-13 может вызывать выраженную гиперреактивность гладких мышц дыхательных путей человека, и сочетанная блокада активности этих цитокинов человеческим моноклональным антителом, нацеленным на общую α-субъединицу рецептора ИЛ-4/ИЛ-13 дупилумаба обусловливает клиническую эффективность не только в отношении обострений и контроля симптомов БА, но и улучшения функции легких и уменьшения бронхиальной гиперреактивности. При

For correspondence

Natalia M. Nenasheva,
2/1 bld. 1, Barrikadnaya ul., Moscow, 125993,
Russian Federation.
E-mail: 1444031@gmail.com
ORCID: https://orcid.org/0000-0002-3162-2510

Для корреспонденции

Ненашева Наталья Михайловна,
Российская Федерация, 125993, Москва,
ул. Баррикадная, 2/1, стр. 1.
E-mail: 1444031@gmail.com
ORCID: https://orcid.org/0000-0002-3162-2510

Статья поступила 22.05.2020 г.
Received: 22.05.2020.
Принята к печати 24.06.2020 г.
Accepted: 24.06.2020.
Рекомендована к публикации
Е.С. Феденко

взаимодействии Т-лимфоцитов хелперов 2-го типа (Th2) и антиген-презентирующих клеток высвобождаются одновременно ИЛ-4 и ИЛ-13, поэтому блокирование ИЛ-4Rα более эффективно, чем блокада каждого из лигандов по отдельности, что объясняет высокую эффективность дупилумаба не только при Т2 астме, но и других Т2-ассоциированных заболеваниях: атопическом дерматите и хроническом полипозном риносинусите. Помимо астмы и атопического дерматита недавно зарегистрировано новое показание для дупилумаба – хронический полипозный риносинусит.

Согласно рекомендациям Европейской Академии Аллергологии и Клинической Иммунологии (EAACI) по биологической терапии ТБА 2020, дупилумаб рекомендуется в качестве дополнительной поддерживающей терапии у взрослых и детей 12–17 лет с неконтролируемой тяжелой Т2 астмой, включая астму аллергического и эозинофильного фенотипа, а также сочетанную (когда присутствуют признаки того и другого фенотипа) и гормонозависимую. При этом отмечена хорошая переносимость препарата.

Ключевые слова: Т2 астма, тяжелая астма, Т2-ассоциированные заболевания, интерлейкины-4 и -13, биологическая терапия, дупилумаб

Для цитирования: Ненашева Н.М. Т2 астма и Т2-ассоциированные заболевания: единый подход к лечению с помощью биологической терапии //*Российский Аллергологический Журнал. 2020. Т. 17. № 3.* С. 34–49.
DOI: https://doi.org/10.36691/RJA1390

Modern therapy with biological drugs or small molecules targeting certain mediators or inflammatory pathways is a promising area of treatment for severe allergic diseases, including bronchial asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, and chronic urticaria. The pathogenesis of allergic diseases involves a complex and still incompletely known mechanism, including genetic factors, cells of innate and adaptive immunity, epithelial barriers, cytokines and chemokines, neurotransmitters and many other cellular and mediator elements that form various phenotypes and endotypes of the disease. These phenotypes and endotypes are constantly modulated and can change under the influence of external and internal factors, such as epigenetic factors, exposome, and microbiome [1]. In this regard, questions arise about the possibility of overcoming the redundancy of a certain inflammatory pathway by blocking one cytokine or one receptor, as well as the choice of this key receptor/cytokine. The issue of selecting patients with severe asthma, who will most optimally respond to a particular biological product, as well as the choice of biomarkers and additional criteria for prognostic efficacy, is still relevant. Evaluation of the efficacy of therapy with biological drugs in relation to various outcomes of asthma can serve as a reference for selection of a particular biological molecule. Some of these issues are discussed in this article.

T2-Associated Diseases

T2 asthma, T2 inflammation, T2-associated diseases are terms that have recently came into the use of specialist medical practitioner: allergists/immunologists, pulmonologists, dermatovenereologists and otorhinolaryngologists. These terms take roots in recent advances in our understanding of the mechanisms of asthma and some related conditions (allergic rhinitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis), as complex heterogeneous diseases with different, but interrelated immune inflammatory pathways, continuously modified under the influence of many external and internal factors [2–6]. Severe asthma accounts for a small proportion (3–10%) of all cases of bronchial asthma (BA) and, like all BA types, is heterogeneous. The characteristics of different phenotypes of severe BA include clinical symptoms, functional parameters, morphological and inflammatory indicators, and microbiome-related characteristics; however, they do not always reflect the underlying pathogenetic mechanism that the endotypes best characterize. As defined by G.P. Anderson [2], a disease endotype is a subtype of the disease defined by a unique or distinctive functional or pathophysiological mechanism. One BA endotype can underlie several phenotypes, since an endotype forms the molecular basis of phenotypes. To investigate the molecular endotypes of BA, a study was carried out of the gene expression of main surrogate markers of T2 inflammation mediated by cytokines IL-13/IL-4 (CLCA1, periostin, and serpin B2) by epithelial cells of the bronchial mucosa, which were obtained by bronchoscopy and biopsy of the bronchial mucosa of "naive" patients (i.e. not treated with anti-inflammatory therapy for asthma) with mild and moderate to severe asthma and healthy subjects (control group) [7, 8]. This study showed that about half of BA patients had high expression levels of these genes, while the rest had the same levels as in healthy subjects. Further study of the genes of interleukins (IL)-13 and IL-5 using a quantitative polymerase chain reaction confirmed the hypothesis that the population of BA patients is heterogeneous: some had

DOI: https://doi.org/10.36691/RJA1390

high T2 inflammation in the mucous membrane, while others had low T2 inflammation. In addition to Th2 cells, recently discovered innate immunity cells, ILC2 (type 2 innate lymphoid cells), are involved in the formation of eosinophilic inflammation in BA, which, like Th2 cells, generate an excessive amount of T2 cytokines: IL-4, IL-5, IL-13. Therefore, the name of this type of inflammation and BA endotype was changed from Th2, which implied the production of these cytokines exclusively by Th2 lymphocytes, to type 2 inflammation (T2 inflammation), which, accordingly, underlies T2 asthma [9].

The main immune inflammatory mechanisms of severe BA (SBA) include endotypes with high T2 inflammation (T2 asthma), low T2 inflammation (non-T2 asthma) and mixed endotypes, which may have common genetic, epigenetic, metabolic, neurogenic, and remodeling characteristics [3, 10–12].

According to research results, the majority of patients with severe asthma (55–77%) belong to the T2 asthma endotype and have eosinophilic inflammation in the mucous membrane of the lower respiratory tract [13–15]. T2 asthma is associated with an eosinophilic and/or allergic phenotype, in which inflammation is caused by increased expression of type 2 cytokines (T2 cytokines). T2 cytokines include interleukins (IL) 4, 5 and 13. These are key cytokines that play a major role in the pathogenesis of type 2 inflammation, which underlies the development of T2-associated diseases: bronchial asthma, allergic rhinitis (AR), atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps (CRSwNP), aspirin-exacerbated respiratory disease (AERD), eosinophilic esophagitis, eosinophilic COPD [16–22]. When determining the T2 endotype of asthma, the attention should be paid to blood eosinophilia, tissue eosinophilia, increased serum levels of immunoglobulin (Ig) E, nitric oxide levels in exhaled air, the presence of concomitant diseases of the nose and paranasal sinuses, atopic dermatitis.

The key and central role of IL-4 and IL-13 in the pathogenesis of T2-associated diseases

Given the important role of IL-4 and IL-13 in the regulation of T2 inflammation, various targeted molecules have been investigated over the past 20 years, but none of them has demonstrated significant clinical efficacy. However, the results of clinical studies of dupilumab, a human recombinant monoclonal antibody (immunoglobulin G4 (IgG4)) against the interleukin-4 receptor subunit α (IL-4Rα), which is common to the IL-4 and IL-13 receptors, have confirmed that IL-4 and IL-13 play a key role in the regulation of T2 inflammation (Fig. 1). Interleukin-13 is a key cytokine that plays an important role in the induction of inflammation and remodeling due to stimulation of mucous hypersecretion by goblet cells, fibrosis, smooth muscle changes, and the development of airway hyperresponsiveness [23, 24]. Activation of IL-4 and, to a lesser extent, IL-13 switches the production of immunoglobulins by B cells towards an increase in the production of IgE and IgG4 in humans and IgG1 in mice [25–27]. Both cytokines (IL-4 and IL-13) promote the migration of eosinophils from the bloodstream to inflammatory foci due to the production of various factors, including IL-5 and eotaxin, by type 2 T-helper cells (Th2) and epithelial cells [28]. Due to the overlapping functions of IL-4 and IL-13, the contribution of each of these cytokines to the implementation of the T2 immune response and T2 inflammation is still poorly understood.

In this regard, a recent experimental study determined the role and specifics of the interaction of IL-4 and IL-13 in the development of T2-inflammation in a mouse model and clarified the mechanism of action of

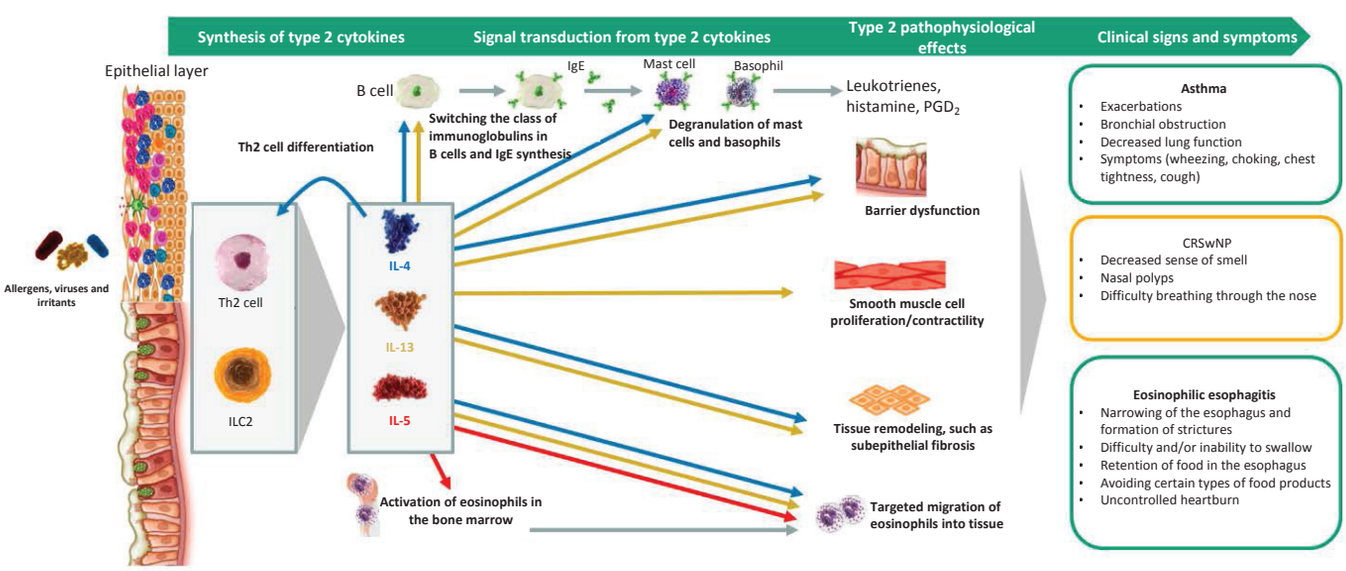


Fig. 1. IL-4 and IL-13 are the main and central type 2 cytokines that determine the pathophysiological mechanisms of the development of T2 inflammation (adapted from Gandhi NA et al., 2017 [16])

DOI: https://doi.org/10.36691/RJA1390

dupilumab [29]. Mice received 10 μg of IL-4 or IL-13 intranasally for 12 days or 50 μg of house dust mite allergen (HDMA) 3 times a week for 4 weeks. Mice exposed to HDMA were divided into groups that either did not receive antibodies (Ab), or received anti-IL-4Rα Ab (dupilumab) 10 or 25 mg/kg 2 times a week, or anti-IL-4 Ab, or mouse IL-13Rα2-Fc, or isotype-matched control Abs (human IgG4 or mouse IgG2α). Antibodies were administered 3 days before the HDMA challenge or on the day of HDMA challenge in the FlexiVent experiment (respiratory function assessment equipment). The results showed that both cytokines, IL-4 and IL-13, are capable of inducing pulmonary inflammation. Intranasal administration of IL-4 and IL-13 results in the development of an asthma-like phenotype in mice. Infiltration of the lungs with immune cells ($CD45^+$), especially $CD4^+$ T cells, increased with intranasal administration of IL-4 and IL-13, while the number of immune cells circulating in the bloodstream did not increase. Administration of IL-13 and, to a lesser extent, IL-4 resulted in a significant decrease in the number of alveolar macrophages in the lung tissue, reflecting a disruption of the epithelial barrier. IL-4 and IL-13 also promoted the influx of eosinophils and neutrophils to the lung tissue. Exposure to IL-4 and IL-13 resulted in an increase in the production of cytokines IL-6 and IL-33, as well as T2 cytokines IL-4, IL-5, IL-13. The expression of chemokines involved in the mobilization of inflammatory cells also increased under the influence of IL-4 and IL-13. IL-13 and, to a lesser extent, IL-4 promoted the development of goblet cell hyperplasia [29]. By comparing inhibitors to ligands for each of the cytokines and double inhibition, it was demonstrated that IL-4 inhibition prevents B-cell activation, IgE production, differentiation of innate immunity cells with $Fc_{\varepsilon}RI$ expression, tissue infiltration with T cells, while IL-13 inhibition prevents goblet cell hyperplasia. It has been shown that it is the blockade of IL-4Rα with dupilumab, but not IL-4 and IL-13 separately, that is required to prevent Th2 activation of antigen presenting cells (APC) in vitro and prevent pulmonary eosinophilia and the production of inflammatory cytokines and chemokines in the lungs in vivo. In addition, dual inhibition of IL-4/IL-13 reduces HDMA-induced activation of B cells both in the lungs and in the systemic circulation, but leads to a decrease only in tissue eosinophilia, not affecting eosinophils circulating in the blood. During the experiment, some mice showed a tendency to an increase in eosinophil counts in the pulmonary circulation, which is consistent with the temporary change in eosinophil counts in the blood observed in some patients [30, 31]. It is important to note that blockade of IL-4Rα with dupilumab leads to a significant decrease in the number of asthma exacerbations and an improvement in the lung function, which means that blood eosinophilia does not always correlate with tissue eosinophilia, and it is eosinophilic tissue infiltration that determines the course of the disease. Dual inhibition of IL-4/IL-13 with dupilumab prevents HDMA-induced impairment of the lung function in mice (Fig. 2) [29].

Thus, the experiments carried out showed that dupilumab binds with high affinity to the IL-4Rα subunit, preventing binding of IL-4 and IL-13 to this receptor, which disrupts the signaling pathways of these cytokines, which, in turn, explains the clinical efficacy of the drug for the treatment of T2-inflammation-associated diseases [17, 18, 20, 22, 30, 31]. Since IL-4 and IL-13 simultaneously release due to the interaction between Th2 and APCs, blocking IL-4Rα is more effective than blocking each of these ligands separately [29].

The role of IL-4 and IL-13 in the formation of bronchial hyperresponsiveness

Bronchial hyperresponsiveness (BH) is the main feature of inflammation and clinical manifestation of BA; all therapeutic strategies in BA are aimed at reducing inflammation and decreasing BH. The results of clinical studies and real practice demonstrate that biological drugs targeting T2 cytokines (IL-5 or the alpha-subunit of the IL-4/13 receptor (IL-4Rα)) contribute to a reduction in the frequency of BA exacerbations in patients with type 2 inflammation. However, it was unknown whether these drugs could affect BH. A recently published article sheds light on this issue [32]. The authors of the study performed experimental work on isolated human airways and relied on the hypothesis that inflammatory mediators can directly affect the reactivity of smooth muscles of the respiratory tract. IL-13 is most associated with this form of hyperresponsiveness, since studies on mice and rabbits showed that IL-13 increased bronchoconstriction in rabbits. Similar effects were found for IL-5, IL-17A, and IL-4 in other animal models.

The objective of the study was to investigate the effect of IL-13, presumably capable of causing BH, on the function of smooth muscles of the small airways in humans and to compare these effects with those of IL-4, IL-5 and IL-17A under the same conditions. To study the contractile response of isolated human bronchi, the method of organ culture was used (lung tissue obtained as a result of lobectomy in 33 patients with various lung neoplasms (9 men, 24 women; mean age 69 years (44–82 years)), in which isolated human respiratory tracts were exposed to a controlled effect of inflammatory mediators [32]. The study showed that the addition of IL-13 to the culture caused a 2.4-fold an increase in bronchoconstrictor potency of histamine in comparison with bronchi treated with control solution (pEC_{50} 6.8±0.1 versus 6.4±0.1; $p<0.01$). IL-4, like IL-13, increased 5.1 times the ability of histamine to induce contraction of bronchial muscles (pEC_{50} 6.8±0.1 versus 6.1±0.1; $p<0.05$) and mobilization of intracellular calcium. In contrast, culturing with IL-5 or IL-17A did not affect these histamine effects (pEC_{50}

DOI: https://doi.org/10.36691/RJA1390

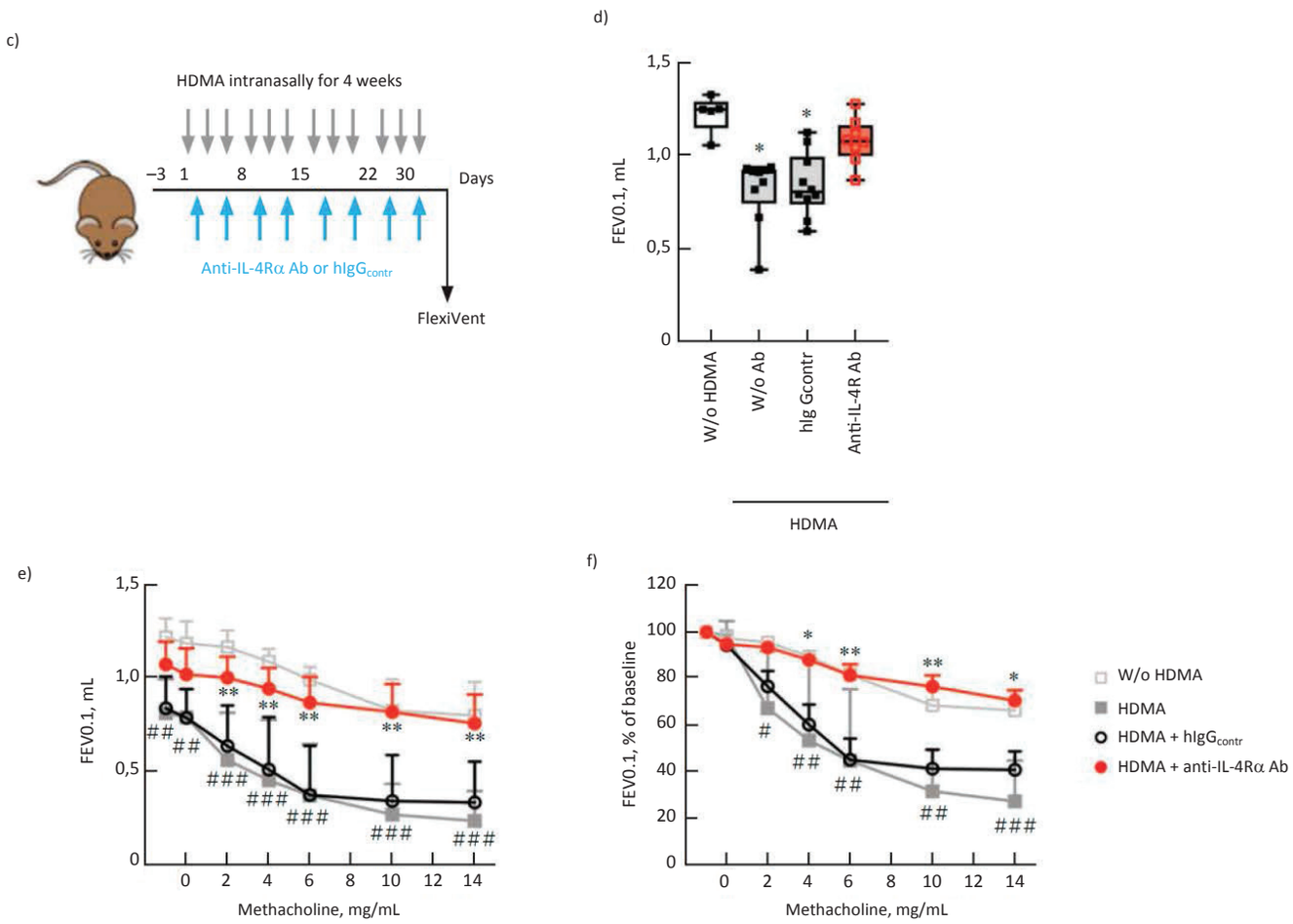


Fig. 2. Dual inhibition of IL-4/IL-13 prevents HDMA-induced impairment of the lung function (c – genetically modified mice were challenged with HDMA or saline for 4 weeks. Two groups of mice exposed to HDMA were subsequently injected with hIgGcontr or anti-IL-4Rα antibodies; d–f – 72–100 h after the last exposure to HDMA, pulmonary function and airway hyperresponsiveness in mice were assessed using negative pressure-driven forced expiratory maneuvers (NPFE) and the forced oscillation technique (FOT) on the FlexiVent platform. After registration of the baseline parameters (d), the mice received increasing doses of methacholine via a nebulizer, for 10 seconds each (0; 2; 4; 6; 10 and 14 mg/mL), after which the functional parameters were measured again (e, f). For each dose of methacholine, FEV0,1 is presented in absolute figures (e) and in relation to the baseline (f) (n≥5 mice in the group); d – * p<0.01 compared with mice that were not exposed to HDMA; e, f – # p<0.1; ## – p<0.01; ### – p<0.001 for mice not exposed to HDMA, compared to mice exposed to HDMA; * – p<0.01; ** – p<0.001 for anti-IL-4Rα antibodies compared to groups treated with IgG control (other significant comparisons not shown), adapted from [29]

6.3±0.2 and 6.4±0.2) compared to control solution (pEC$_{50}$ 6.2±0.1) and histamine-induced mobilization of intracellular calcium [32]. RNA sequencing and an expression analysis using real-time polymerase chain reaction showed that both IL-4 and IL-13 induced an increased expression of histamine and leukotriene D4 (LTD4) receptors. The next series of experiments investigated the influence of dexamethasone and dupilumab on the effects of IL-13 in the bronchi and smooth muscle cells of the human respiratory tract. Dexamethasone and the selective STAT6 inhibitor, AS1517499, did not affect the effects induced by IL-13. In contrast, pretreatment with the IL-4Rα inhibitor dupilumab significantly inhibited the response to IL-4 and IL-13 (Fig. 3), further confirming that the observed effects were due to the activation of common receptors for these cytokines [32]. Probably, the effects of corticosteroids (CSs) can be associated with their ability to suppress the production of anti-inflammatory mediators, while the effects of cytokines are not affected by CSs.

The simultaneous suppression of the effects of IL-13 and IL-4 with dupilumab in clinical trials led to a significant reduction in the frequency of exacerbations of severe asthma, improvement of the pulmonary function, control of asthma and a decreased need for oral CSs in patients with uncontrolled asthma and corticosteroid-dependent asthma [30, 31]. The dupilumab effect does not depend on the presence of CSs, which was confirmed in the above mentioned study, when dexamethasone had no effect on IL-13-induced BH [32]. The study of the effect of IL-5 and IL-17A demonstrated neither an increase in the contractile response of small airways, nor calcium

DOI: https://doi.org/10.36691/RJA1390

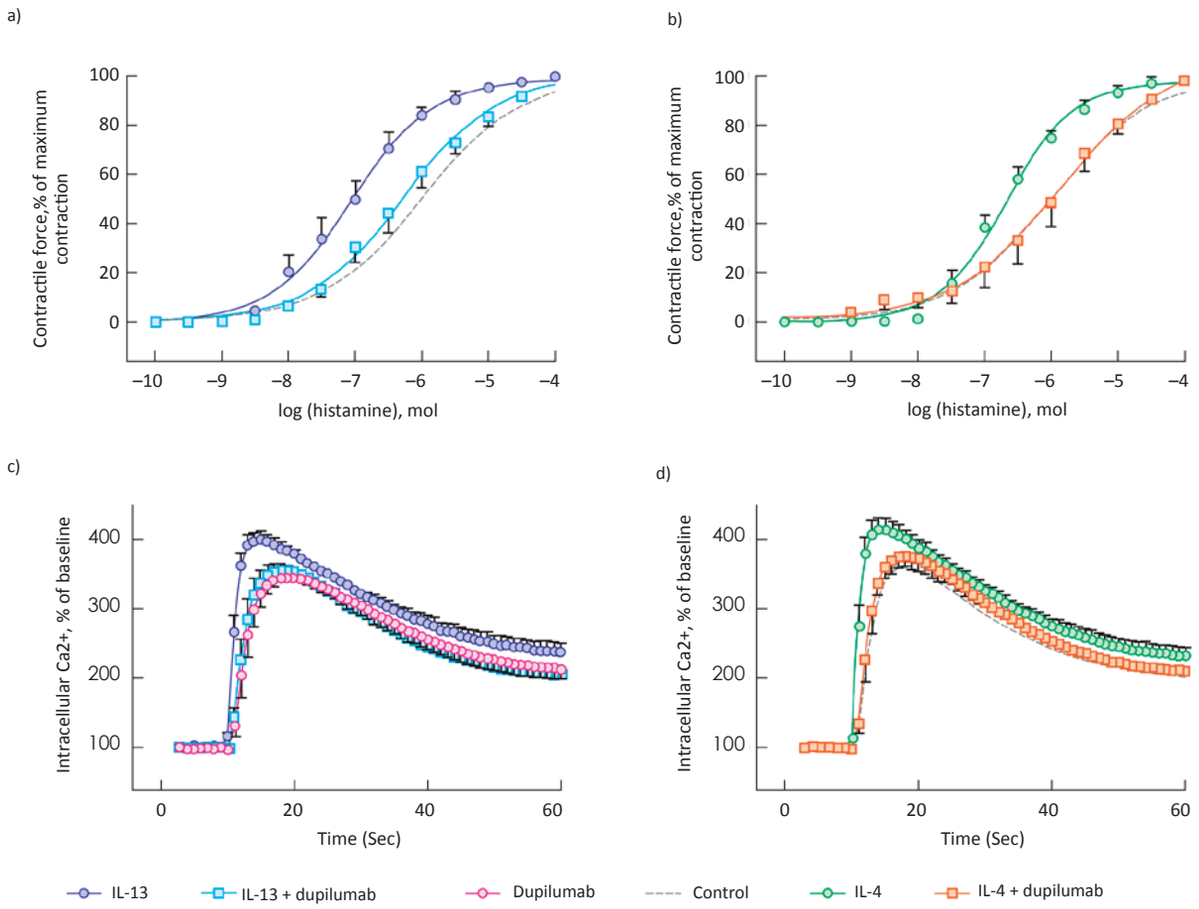


Fig. 3. Effect of dupilumab on BH stimulated by IL-13 and IL-4. Cumulative concentration-response curves were obtained for histamine in human bronchial rings treated for 2 days with IL-13 (a) and IL-4 (b) with and without dupilumab (1 μmol). Statistical comparison of the cytokine pEC_{50} in human bronchial rings treated with dupilumab and in bronchial segments treated with IL-13 and IL-4 was performed using the paired t-test; a – $p<0.01$; b – $p<0.05$. Maximum induction of intracellular calcium by histamine in human airway smooth muscles treated with IL-13 (c) or IL-4 (d) for 24 h with or without dupilumab. Data are presented as mean ± standard error of the mean [32]

mobilization from intracellular stores, nor the expression of receptors [32]. The authors of this study explain the difference between these results and those obtained earlier by the fact that their study used small bronchi of the 8–13th generation, while previous studies used bronchi of the 1–5th generation. Considering the effectiveness of antibodies to IL-5 in the treatment of BA, the study findings confirm that their effect on exacerbations and other outcomes of BA is the result of the effect on eosinophils, rather than a direct effect on the bronchial smooth muscles. This can also explain an insignificant effect of anti-IL-5 antibodies on the lung function [32].

Thus, this study showed that the activation of IL-4/IL-13 can cause pronounced hyperresponsiveness of the smooth muscles of the human respiratory tract, which in turn means that these two cytokines directly contribute to the development of BH and dual blockade of the activity of these cytokines by dupilumab provides the clinical efficacy not only in relation to exacerbations of asthma, but also improvement of the lung function and a reduction in bronchial hyperresponsiveness.

Dupilumab mechanism of action

Dupilumab is a recombinant, fully human monoclonal antibody (MAT) that targets the α-subunit of the IL-4 receptor; thereby blocking the pathways of IL-4 and IL-13, key cytokines in T2 inflammation. The mechanism of action of dupilumab, already mentioned several times above, consists in the binding of the drug to the IL-4Rα-subunit common to the IL-4 and IL-13 receptor complexes, thus it blocks the signaling pathways of both IL-4 and IL-13 and inhibiting the following activation of JAK/STAT and thereby leading to a decrease in the T2-mediated inflammatory cascade (Fig. 4). Blocking the IL-4/IL-13 signaling pathway with dupilumab in patients lowers concentrations of many type 2 inflammation mediators, including immunoglobulin E, periostin, and multiple pro-inflammatory cytokines and chemokines (e.g., eotaxin, thymus- and activation-regulated chemokine (TARC)), and reduces a fraction of exhaled nitric oxide (FeNO) – a marker of inflammation in the lungs. It has already been discussed above that blocking the IL-4/IL-13 signaling pathway

DOI: https://doi.org/10.36691/RJA1390

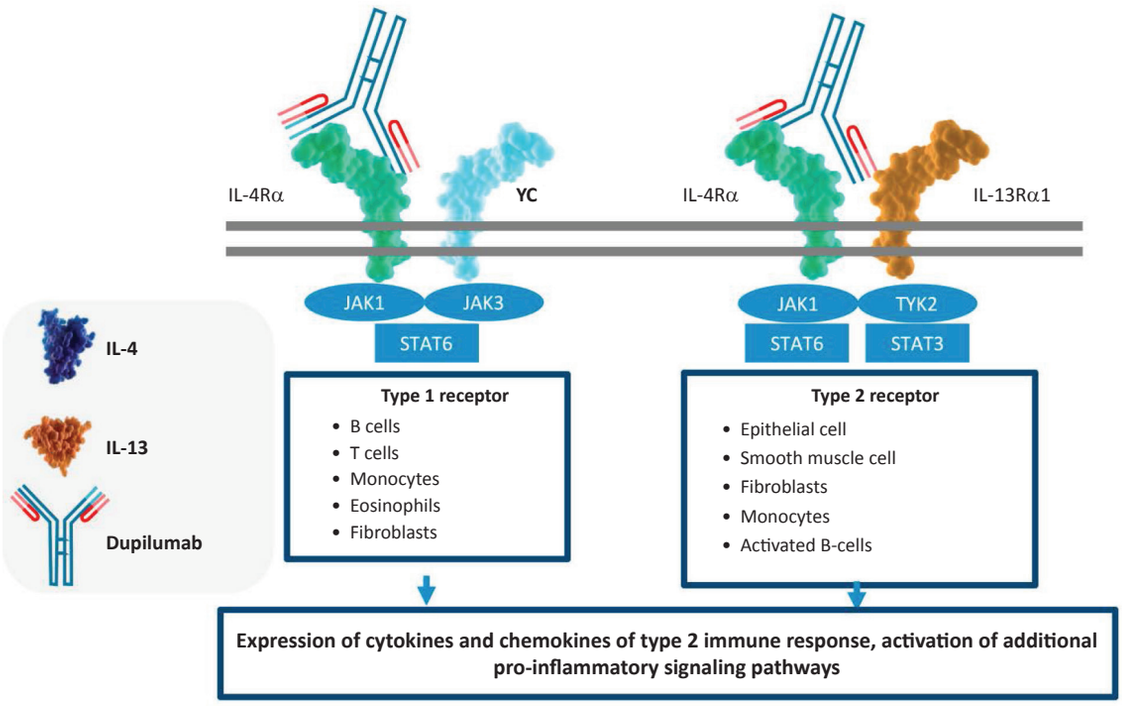


Fig. 4. The main mechanism of action of dupilumab (adapted from Gandhi NA et al., 2016 [33]; JAK1,2,3 – Janus kinases; TYK2 – tyrosine kinase; STAT – transcription factors)

with dupilumab in humanized animal models prevents subsequent effects of these cytokines and chemokines, including goblet cell hyperplasia, hyperresponsiveness of airway smooth muscle cells, eosinophilic inflammation in the lungs, and other inflammatory processes in the lungs, and also prevents impairment of the lung function; at the same time, severity of eosinophilic inflammation in the lungs decreases regardless of normal or increased blood eosinophil counts [29, 32].

Efficacy and safety of dupilumab in patients with bronchial asthma

To assess the efficacy and safety of dupilumab in patients with BA, three randomized, double-blind, placebo-controlled, multicenter, parallel-group studies (DRI12544, QUEST and VENTURE) lasting from 24 to 52 weeks were conducted, involving 2888 patients (aged 12 years and older). Patients were enrolled in all three studies regardless of baseline eosinophil counts or other biomarkers of type 2 inflammation (eg, FeNO or immunoglobulin E levels).

A pivotal phase 3 study QUEST was a 52-week, randomized, double-blind, placebo-controlled study assessing efficacy of dupilumab [30] in patients aged ≥12 years with moderate to severe asthma, not controlled on medium or high dose (fluticasone propionate ≥500 μg/day or equivalent) inhaled corticosteroids (iCSs) in combination with one or two additional maintenance drugs (LABA or leukotriene receptor antagonist). In addition, all patients had one or more exacerbations of

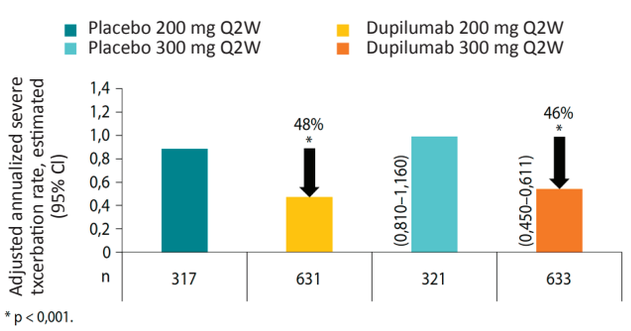


Fig. 5. Dupilumab significantly reduced the frequency of severe exacerbations in patients with uncontrolled persistent bronchial asthma (adapted from [30])

asthma that required the use of systemic corticosteroids or hospitalization/emergency visits in the previous year. Dupilumab was prescribed as adjunctive therapy at a dose of 200 or 300 mg subcutaneously (SC) every other week (Q2W). The co-primary endpoints of the QUEST study were an annual rate of severe exacerbations and an absolute change in FEV1 at 12 weeks versus the baseline. The secondary endpoints of the study were the same parameters in patients with eosinophil counts of ≥150 cells/μL and ≥300 cells/μL. Treatment with dupilumab resulted in a pronounced decrease in the frequency of severe exacerbations of asthma compared with placebo: by 48% in patients treated with 200 mg and by 46% in patients treated with 300 mg (Fig. 5). An analysis depending on the severity of blood eosinophilia in patients showed that a more pronounced decrease in the annual frequency

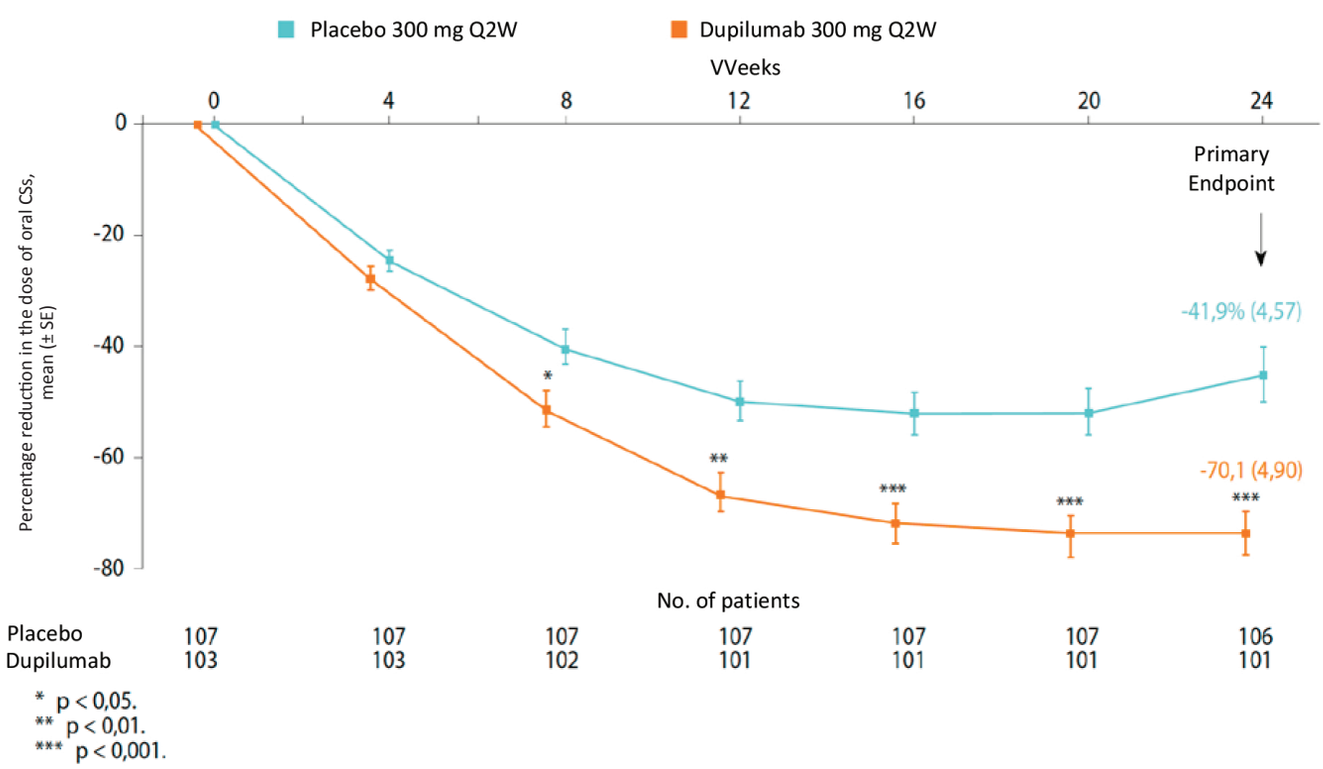
DOI: https://doi.org/10.36691/RJA1390

of severe exacerbations was observed in the subgroup of patients with a baseline eosinophil count of ≥300 cells/μL (a 66–67% decrease compared to the corresponding placebo) [30]. Dupilumab caused a rapid improvement in the lung function as measured by pre-bronchodilator FEV1, and the difference between dupilumab and the corresponding placebo at the first assessment as early as 2 weeks was statistically significant ($p<0.001$) for both doses of the drug. The improvement in the lung function was persistent, with statistically significant differences between dupilumab and placebo determined across all efficacy assessments over the 52-week treatment period. The most pronounced improvement in FEV1 was observed in the subgroup of patients with a baseline eosinophil count of ≥300 cells/μL (the change compared with placebo was 0.21 L and 0.24 L for dupilumab 200 mg Q2W and 300 mg Q2W, respectively; the change from the baseline was 0.43 L and 0.47 L, respectively) [30]. Patients treated with dupilumab experienced an improvement in BA control according to ACQ-5.

Dupilumab was well tolerated, and the frequency of adverse events was similar between the placebo and dupilumab groups. Injection site reactions (mainly hyperemia, sometimes with itching) occurred more often in the dupilumab groups than in the placebo groups (15% and 5% [200 mg Q2W]: 18% and 10% [300 mg Q2W]), which was consistent with the data of phase 2 clinical studies of dupilumab in asthma. Based on our own experience, these reactions occur in patients more often at the beginning of therapy, are moderate and, as a rule, resolve on their own after a short time. The frequency of these reactions decreases with continued therapy.

The VENTURE study [31] evaluated the effect of dupilumab on reducing the use of maintenance oral corticosteroids. The initial mean oral corticosteroid dose was 11.75 mg in the placebo group and 10.75 mg in the dupilumab group. Compared with placebo, patients treated with dupilumab achieved a greater reduction in the daily dose of oral corticosteroids (OCS) while maintaining asthma control. The mean overall decrease in a daily OCS dose while maintaining asthma control was 70.1% compared to the baseline in patients receiving dupilumab and 41.9% in the placebo group (Fig. 6) [31]. It is important that after 24 weeks, severe exacerbations of asthma were recorded 59% less frequently in the dupilumab group than in the placebo group, and there was a statistically significant improvement in the lung function with a simultaneous dose reduction or complete discontinuation of OCS.

Thus, the phase 3 studies Liberty Asthma QUEST and VENTURE showed that dupilumab significantly reduced the annual rate of severe asthma exacerbations, significantly improved the lung function, and led to improved quality of life and asthma control manifested as a pronounced decrease in the dose of oral corticosteroids



Note. CSs – corticosteroids.

Fig. 6. The study of a steroid-sparing effect (VENTURE): a statistically significant decrease in the need for OCS compared to placebo at week 24 in the general population while using dupilumab (adapted from [31])

DOI: https://doi.org/10.36691/RJA1390

while reducing the frequency of exacerbations and improving the lung function. At the same time, dupilumab was well tolerated by adults and adolescents with uncontrolled persistent and corticosteroid-dependent asthma.

An analysis of the results of clinical studies showed that the most pronounced improvement in the lung function and a decrease in the frequency of exacerbations due to dupilumab treatment was observed in patients with high levels of two type 2 biomarkers (baseline blood eosinophil count of ≥150/μL and baseline FeNO level of ≥25 ppb), while blood eosinophil counts did not affect the efficacy of dupilumab in corticosteroid-dependent asthma.

Results of using dupilumab in real clinical practice

The experience with the drug in real clinical practice is very important, which makes it possible to solve the critical question of whether the drug works under conditions of greater heterogeneity of patient characteristics, in different medical institutions and settings. Routine practice study results complement and expand RCT findings. Such a study with dupilumab was carried out in France under the early access and temporary authorization for use (ATU) program for patients with severe asthma [34]. The authorization was granted to 86 patients with severe BA. T2 biomarkers were not taken into account when selecting patients. The program did not include patients with a blood eosinophil count of ≥1500 cells/μL in the previous 12 months. Prior to inclusion in the study, signs of severe uncontrolled asthma persisted despite previous therapy. All patients received inhaled CSs at 1200 μg/day. 73.4% of patients continued to receive systemic CSs daily. The average dose of prednisolone was 20 mg/day. 11.7%, 95% and 17.7% of patients received various immunosuppressive drugs, long-acting beta-agonists (LABA), and azithromycin, respectively. The majority of patients received treatment with monoclonal antibodies, omalizumab (83.9%) and mepolizumab (16.7%), prior to inclusion in the study. Four patients underwent bronchial thermoplasty. Dupilumab was injected subcutaneously: 600 mg on the first day, then 300 mg every two weeks for 12 months. On average, four BA exacerbations were recorded in patients in the previous year; 28 (43.7%) patients were hospitalized over the last 12 months. The average level of BA control according to ACT (Asthma Control Test) was 14 and indicated uncontrolled BA. According to functional tests, the patients had signs of obstructive respiratory dysfunction and decreased FEV1 values. The total IgE level was above normal. In half of the cases, the level of eosinophils was 150 cells/μL and higher.

As a result of therapy, dupilumab significantly improved the ACT score by the third month of treatment. Improvement persisted at six months of therapy. At 12 months, the ACT score was 22 points (the difference from the baseline value of 8.5 points). Moreover, the control level exceeded 20 points in 25% of patients at three months of therapy. At 12 months of therapy, the proportion of such patients reached 51%. The frequency of asthma exacerbations is an important characteristic of the efficacy of therapy. Dupilumab significantly reduced the frequency of exacerbations and improved the lung function after 12 months of treatment. Patients had four exacerbations per year at the baseline and one after 12 months of dupilumab therapy (Fig. 7). In addition, patients' lung function significantly improved (Fig. 7) [34].

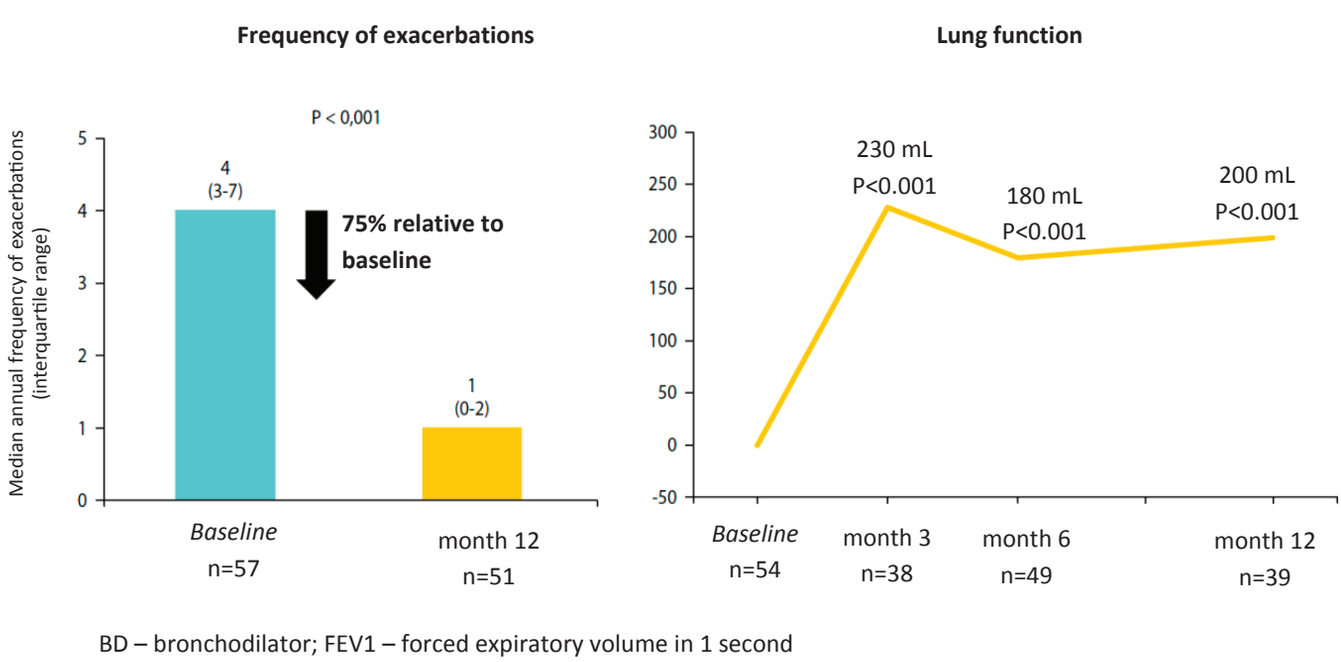


Fig. 7. A reduction in the frequency of exacerbations and improvement of the lung function (adapted from [34])

The use of dupilumab allowed reducing the dose of oral corticosteroids. On average, at 12 month of therapy, the dose was reduced from 20 to 6 mg/day without the patient's condition worsening. Approximately 50% of patients discontinued oral corticosteroids by month 12 of dupilumab therapy. According to the physician (GETE), an excellent or good effect of treatment was observed in 60% of patients at three months after its initiation and in 78% at 12 months [34]. During the follow-up, the investigators drew attention to one important point: eosinophilia is often found in this group of patients. An increase in blood eosinophil counts of 1500 cells/μL and greater was recorded in 25% of patients. However, hypereosinophilia was not accompanied by a worsening of clinical symptoms and did not lead to discontinuation of therapy. Moreover, the therapy had similar effects in patients with eosinophil counts of >1500 cells/μL and patients with lower eosinophil counts. After analyzing the data obtained, the researchers concluded that the clinical effects (according to FEV1, ACT score, the use and dose of oral CSs, proportion of GETE score 1–2) at 12 months did not change depending on the baseline blood eosinophil counts. Previous treatment with monoclonal anti-IgE or IL-5 antibodies also did not affect the outcomes of treatment with dupilumab [34].

for the biological therapy of severe asthma were published only recently [12]. In the Guidelines, experts, following the GRADE (The Grading of Recommendations Assessment, Development and Evaluation) approach, i.e. method for assessing the validity and quality of evidence and the strength of recommendations, identified recommendations for each biologic and each outcome. In addition, an algorithm is proposed for selecting biological therapy and managing patients after prescribing the drug. The response to biological therapy is assessed at 4 months, and if necessary, the treatment is continued with reevaluation every 3–6 months. If in 4–6 months the doctor and the patient note a clinical effect according to predetermined outcomes (exacerbations, lung function, dose reduction of oral or inhaled corticosteroids, control of asthma and/or comorbidities), then therapy should be continued and safety parameters monitored [12]. Experts emphasize that the primary criteria for assessing the efficacy of biological therapy are: severe asthma exacerbations, asthma control, quality of life, safety (adverse events). Important criteria for assessing the efficacy of biological therapy: FEV1, dose reduction of oral or inhaled CSs. FeNO, sputum eosinophils and blood eosinophils were scored as low importance criteria. The tables below provide recommendations for the use of dupilumab in patients with asthma, depending on different outcomes and strength of recommendations, according to the EAACI Guidelines on the use of biologicals in severe asthma [12].

Table 1. Recommendations for the use of dupilumab as an add-on maintenance therapy in adults and children aged 12–17 years old with uncontrolled severe eosinophilic asthma (adapted from [12])

1. Dupilumab is recommended in adults and children aged 12–17 years old with uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function**	Strong recommendation
	Reduce the rescue medication use**	Conditional recommendation
2. Dupilumab has shown a favorable safety profile, however long-term safety data (up to 2 years) are extrapolated from studies in patients with atopic dermatitis; careful reporting of adverse drug reactions is recommended		Conditional recommendation

Note. * – Population: severe asthma not controlled by medium/high doses of iCS, plus up to 2 additional controller drugs, including oral CS; T2 inflammation (according to the EMA requirements), characterized by an increase in blood eosinophil levels (>150 cells/μL) and/or an increase in FeNO >20 ppb; ** – population: a subgroup of adults with blood eosinophils >300 cells/μL or FeNO level >50 ppb; *** – although the size of the effect is small, it may be justified in patients at increased risk of complications due to the drug use; FeNO – fraction of exhaled nitric oxide; iCS – inhaled corticosteroids; oCS – oral corticosteroids; EMA – European Medical Agency.

Thus, the results of a dupilumab study in real clinical practice confirmed its efficacy and safety in patients with severe uncontrolled BA. Dupilumab significantly improves asthma control and the lung function, reduces the frequency of exacerbations and the need for oral CSs. These data are fully consistent with the data on the efficacy and safety from large-scale randomized clinical trials.

The place of dupilumab in the updated 2020 EAACI Guidelines on the use of biologicals in severe asthma

The 2020 Guidelines of the experts of the European Academy of Allergy and Clinical Immunology (EAACI)

Thus, dupilumab is recommended as an add-on maintenance therapy in adults and children aged 12–17 years old with uncontrolled severe T2 asthma, including asthma with the allergic and eosinophilic phenotype, as well as mixed (when there are signs of both phenotypes) and steroid-dependent asthma. However, there is a strong recommendation in respect of outcomes such as decreased severe exacerbations, dose reduction or discontinuation of oral corticosteroids, and improved lung function.

Table 2. Recommendations for the use of dupilumab as an add-on maintenance therapy in adults and children aged 12–17 years old with uncontrolled severe allergic asthma (adapted from [12])

1. Dupilumab is recommended in adults and children aged 12–17 years old with uncontrolled severe allergic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function**	Conditional recommendation
2. Dupilumab has shown a favorable safety profile, however long-term safety data (up to 2 years) are extrapolated from studies in patients with atopic dermatitis; careful reporting of adverse drug reactions is recommended		Conditional recommendation

Note. * – Population: severe asthma not controlled by medium/high doses of iCS, plus up to 2 additional controller drugs, including oral CS; T2 inflammation (according to the EMA requirements), characterized by an increase in blood eosinophil levels (>150 cells/μL) and/or an increase in FeNO >20 ppb; ** – population: a subgroup of adults with blood eosinophils >300 cells/μL or FeNO level >50 ppb; FeNO – fraction of exhaled nitric oxide; iCS – inhaled corticosteroids; oCS – oral corticosteroids; EMA – European Medical Agency.

Table 3. Recommendations for the use of dupilumab as an add-on maintenance therapy in adults and children aged 12–17 years old with uncontrolled severe T2 asthma (adapted from [12])

1. Dupilumab is recommended in adults and children aged 12–17 years old with uncontrolled severe T2 asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Dose reduction or discontinuation of oral corticosteroids**	Strong recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improved lung function***	Strong recommendation
	Reduced rescue medication use**	Conditional recommendation
2. Dupilumab has shown a favorable safety profile, however long-term safety data (up to 2 years) are extrapolated from studies in patients with atopic dermatitis; careful reporting of adverse drug reactions is recommended		Conditional recommendation

Note. * – Population: severe asthma not controlled by medium/high doses of iCS, plus up to 2 additional controller drugs, including oral CS; T2 inflammation (according to the EMA requirements), characterized by an increase in blood eosinophil levels (>150 cells/μL) and/or an increase in FeNO >20 ppb; ** – population: patients with severe corticosteroid-dependent asthma receiving controller therapy with oCSs and high doses of iCSs in combination with a second controller drug; *** – population: a subgroup of adults with blood eosinophils >300 cells/μL or FeNO level >50 ppb or patients with corticosteroid-dependent asthma (controller therapy with oCSs); **** – although the effect size is small, this may be justified in patients at increased risk of side effects due to the drug use; FeNO – fraction of exhaled nitric oxide; iCS – inhaled corticosteroids; oCS – oral corticosteroids; EMA – European Medical Agency.

Efficacy of dupilumab in patients with asthma and concomitant chronic rhinosinusitis with nasal polyps

Epidemiological data support the coexistence of asthma and upper respiratory tract diseases, including allergic rhinitis (AR), chronic rhinosinusitis (CRS) with or without nasal polyposis (NP), aspirin-exacerbated respiratory disease, as well as obstructive sleep apnea and vocal cord dysfunction [35, 36]. CRS symptoms may be present in 22–42% of patients with BA [37]. A strong association has been shown between CRS and asthma (odds ratio, OR 3.47), while the association is stronger in patients with both CRS and BA (OR 11.85) [38]. The history and clinical symptoms of nasal polyps usually precedes asthma, and up to 45% of patients with nasal polyps develop asthma. The prevalence of CRS with nasal polyps is higher in asthma patients (7%) compared with the general population (4%) [39]. The presence of CRS with nasal polyps (CRSwNP) is usually associated with severe, poorly controlled asthma with frequent exacerbations, with more pronounced inflammation in the upper and lower respiratory tract. According to the national registry for severe BA, about 10% of patiens have chronic rhinosinusitis with nasal polyps [40], while its prevalence does not differ between patients with allergic and non-allergic SBA [41].

Analysis of patients included in the QUEST study showed that 22–25% had chronic rhinosinusitis with nasal polyps and/or chronic rhinosinusitis [30]. A sub-

sequent retrospective analysis showed that the use of dupilumab in patients with concomitant CRS/CRSwNP and without CRS/CRSwNP significantly improved FEV1 [42]. In addition, the use of dupilumab significantly reduced the severity of symptoms specific for CRS/CRSwNP and the quality of life compared to placebo, based on the SNOT-22 score (a 22-item Sino-Nasal Outcomes test) [42, 43].

For the first time, the effect of dupilumab on CRSwNP was shown in a study by Bachert et al., in which 60 patients participated [44]. Patients were randomized to receive dupilumab 300 mg (loading dose 600 mg) or placebo. The primary endpoint was the endoscopic nasal polyps score at 16 weeks, which was significantly lower in the dupilumab group ($p<0.001$). Significant improvements were noted according to computed tomography of the sinuses, SNOT-22 and olfaction as secondary endpoints. Subsequent analyses were performed on 35 patients with asthma [45]. In this group, dupilumab was associated with improved asthma control and patients' quality of life.

In June 2019, the FDA (American Food and Drug Administration) approved the use of dupilumab in patients with chronic rhinosinusitis with nasal polyps (CRSwNP). This approval was based on the results of two randomized, double-blind, placebo-controlled studies [45]. The studies included patients with CRSwNP who were refractory to surgical treatment or nasal steroids in the previous two years. The first study involved 276 patients who were randomized to receive either 300 mg dupilumab or placebo every two weeks for 24 weeks in combination with intranasal mometasone furoate. Treatment with dupilumab resulted in a decrease in polyps size according to the endoscopic nasal polyps score, improvement in nasal congestion and other CRSwNP symptoms. This improvement was accompanied by reduced need for systemic steroids or surgery, and was associated with improved FEV1 and asthma control in patients with comorbid asthma [45]. The second long-term study with 448 patients fully replicated these results during 52 weeks of treatment [45].

Dupilumab was approved in September 2019 in the EU countries and on July 17, 2020 in our country.

According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS) [36], biological therapy is recommended for patients with CRSwNP who meet the following criteria. Presence of bilateral polyps, a patient who has had sinus surgery or is not a candidate for surgery and who has three of the following characteristics: signs of T2 inflammation (tissue eosinophils ≥10/per HPF or blood eosinophils ≥250 cells/μL OR total IgE ≥100), the need for at least two courses of systemic corticosteroids or continuous use of systemic corticosteroids (≥2 courses per year OR long-term (>3 months) low-dose corticosteroid courses OR contraindications to systemic steroids), significantly impaired quality of life (SNOT-22 score ≥40), a positive anosmia test, and/or a diagnosis of comorbid asthma requiring regular inhaled corticosteroids [36]. At the same time, the level of evidence for the efficacy of dupilumab is marked as 1a, which means the highest level.

Conclusion

Bronchial asthma is a heterogeneous disorder with a variable course. Identification the pathobiological mechanisms underlying the formation of BA phenotypes, or the so-called BA endotypes, is an urgent task in optimizing BA therapy, especially severe BA. The majority of patients with severe asthma (55–77%) belong to the T2 asthma endotype and have eosinophilic inflammation in the mucous membrane of the lower respiratory tract, with a significant proportion of patients not achieving control on iCS. IL-4 and IL-13 play a key role in the regulation of T2 inflammation, which determines the high efficacy of dupilumab that blocks the common α-subunit of the IL-4/13 receptor in patients with moderate to severe uncontrolled T2 asthma. Dupilumab significantly reduces the frequency of severe asthma exacerbations, improves the lung function, results in an improvement in the quality of life and asthma control, a pronounced decrease in the dose of oral corticosteroids, while reducing the frequency of exacerbations and improving the lung function. At the same time, dupilumab is well tolerated by adults and adolescents with uncontrolled persistent T2 asthma and corticosteroid-dependent BA. Important predictors of response to dupilumab in patients without corticosteroid-dependent asthma include blood eosinophil counts over 150 cells/mm^3 and FeNO greater than 25 ppb (parts per billion). Another factor in favor of dupilumab is the presence of concomitant T2-associated diseases, including atopic dermatitis, chronic rhinosinusitis with nasal polyps, and allergic rhinitis.

Dupilumab is currently indicated:

- as an add-on maintenance therapy for moderate to severe asthma in patients aged 12 years and older with an eosinophilic phenotype or in patients with corticosteroid-dependent asthma, treated with oral CSs;
- for the treatment of moderate to severe atopic dermatitis in patients aged 12 years and older whose disease is not adequately controlled with topical drugs or in the case when such drugs are not advisable; dupilumab can be used with or without topical drugs;
- as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps.

REFERENCES

1. Agache I, Akdis CA. Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases. *J Clin Invest*. 2019;129(4):1493–503. doi: 10.1172/JCI124611

2. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet*. 2008;372(9643):1107–1119. doi: 10.1016/S0140-6736(08)61452-X
3. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol*. 2011;127(2):355–360. doi: 10.1016/j.jaci.2010.11.037
4. Agache I, Akdis C, Jutel M, Virchow JC. Untangling asthma phenotypes and endotypes. *Allergy*. 2012;67(7):835–846. doi: 10.1111/j.1398-9995.2012.02832.x
5. Agache IO. From phenotypes to endotypes to asthma treatment. *Curr Opin Allergy Clin Immunol*. 2013;13(3):249–256. doi: 10.1097/ACI.0b013e32836093dd
6. Agache I, Akdis CA. Endotypes of allergic diseases and asthma: an important step in building blocks for the future of precision medicine. *Allergol Int*. 2016;65(3):243–252. doi: 10.1016/j.alit.2016.04.011
7. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009;180(8):796. Corrected and republished from: *Am J Respir Crit Care Med*. 2009;180(5):388–395. doi: 10.1164/rccm.200903-0392OC
8. Bhakta NR, Woodruff PG. Human asthma phenotypes: from the clinic, to cytokines, and back again. *Immunol Rev*. 2011;242(1):220–232. doi: 10.1111/j.1600-065X.2011.01032.x
9. Nenasheva NM. T2-high and T2-low bronchial asthma, endotype characteristics and biomarkers. *Pulmonologiya*. 2019;29(2):216–228 (In Russ.). doi: 10.18093/0869-0189-2019-29-2-216-228
10. Agache I. Severe asthma phenotypes and endotypes. Semin Immunol. 2019;46:101301. doi: 10.1016/j.smim.2019.101301
11. Agache I, Sugita K, Morita H, Akdis M, Akdis CA. The complex type 2 endotype in allergy and asthma: from laboratory to bedside. *Curr Allergy Asthma Rep*. 2015;15(6):29. doi: 10.1007/s11882-015-0529-x
12. Agache I, Akdis C, Akdis M, Canonica GW, Casale T, Chivato T, et al. EAACI Biologicals Guidelines – Recommendations for severe asthma. *Allergy*. 2020:1–31. doi: 10.1111/all.14425
13. Sergeeva GR, Emelyanov AV, Korovina OV, Znakhurenko AA, Leshenkova EV, Kozyreva LV, Asatiani N. Severe asthma: characteristics of patients in clinical practice. *Terapevticheskii arkhiv*. 2015;87(12):26–31 (In Russ.). doi: 10.17116/terarkh2015871226-31
14. Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir Med*. 2014;108(12):1723–1732. doi: 10.1016/j.rmed.2014.10.007
15. Shau DE, Sousa AR, Fowler SJ, Fleming LJ, Robers G, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. 2015;46(5):1308–1321. doi: 10.1183/13993003.00779-201
16. Gandhi NA, Pirozzi G, Graham NM. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol*. 2017;13(5):425–437. doi: 10.1080/1744666X.2017.1298443
17. Weinstein SF, Katial R, Jayawardena S, Pirozzi G, Staudinger H, Eckert L, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. *J Allergy Clin Immunol*. 2018;142(1):171–177.e1. doi: 10.1016/j.jaci.2017.11.051
18. Jonstam K, Swanson BN, Mannent LP, Cardell LO, Tian N, Wang Y, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. *Allergy*. 2019;74(4):743–752. doi: 10.1111/all.13685
19. Furue K, Ito T, Tsuji G, Ulzii D, Vu YH, Kido-Nakahara M, et al. The IL-13-OVOL1-FLG axis in atopic dermatitis. *Immunology*. 2019;158(4):281–286. doi: 10.1111/imm.13120
20. Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;143:155–172. doi: 10.1016/j.jaci.2018.08.022
21. Markowitz JE, Jobe L, Miller M, Frost C, Laney Z, Eke R. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated for 9 years. *J Pediatr Gastroenterol Nutr*. 2018;66(6):893–897. doi: 10.1097/MPG.0000000000001840
22. Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. *Gastroenterology*. 2020;158(1):111–122.e10. doi: 10.1053/j.gastro.2019.09.042
23. Wynn TA. IL-13 effector functions. *Annu Rev Immunol*. 2003;21:425–456. doi: 10.1146/annurev.immunol.21.120601.141142
24. Corren J. Role of interleukin-13 in asthma. *Curr Allergy Asthma Rep*. 2013;13(5):415–420. doi: 10.1007/s11882-013-0373-9
25. Paul WE. History of interleukin-4. *Cytokine*. 2015;75(1):3–7. doi: 10.1016/j.cyto.2015.01.038
26. Punnonen J, Aversa G, Cocks BG, McKenzie AN, Menon S, Zurawski G, et al. Interleukin-13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B-cells. *Proc Natl Acad Sci U S A*. 1993;90(8):3730–3734. doi: 10.1073/pnas.90.8.3730
27. Gascan H, Gauchat JF, Roncarolo MG, Yssel H, Spits H, de Vries JE. Human B-cell clones can be induced to proliferate and to switch to IgE and IgG4 synthesis by interleukin 4 and a signal provided by activated $CD4^+$ T-cell clones. *J Exp Med*. 1991;173(3):747–750. doi: 10.1084/jem.173.3.747
28. Rosenberg HF, Phipps S, Foster PS. Eosinophil trafficking in allergy and asthma. *J Allergy Clin Immunol*. 2007;119(6):1303–1310. doi: 10.1016/j.jaci.2007.03.048
29. Le Floc'h A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75(5):1188–1204. doi: 10.1111/all.14151
30. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486–2496. doi: 10.1056/NEJMoa1804092.
31. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-depen-

dent severe asthma. *N Engl J Med.* 2018;378(26):2475–2485. doi: 10.1056/NEJMoa1804093
32. Manson ML, Säfholm J, James A, Johnsson AK, Bergman P, Al-Ameri M, et al. IL-13 and IL-4, but not IL-5 nor IL-17A, induce hyperresponsiveness in isolated human small airways. *J Allergy Clin Immunol.* 2020;145(3):808–817.e2. doi: 10.1016/j.jaci.2019.10.037
33. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Vancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov.* 2016;15(1):35–50. doi: 10.1038/nrd4624
34. Bourdin A, Fabry-Vendrand C, Ostinelli J, Ait-Yahia M, Darnal E, Bouee S, et al. The burden of severe asthma in France: a case-control study using a medical claims database. *J Allergy Clin Immunol Pract.* 2019;7(5):1477–1487. doi: 10.1016/j.jaip.2018.12.029
35. Tiotiu A, Plavec D, Novakova S, Mihaicuta S, Novakova P, Labor M, et al. Current opinions for the management of asthma associated with ear, nose and throat comorbidities. *Eur Respir Rev.* 2018;27(150):180056. doi: 10.1183/16000617.0056-2018
36. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology.* 2020;Suppl 29:1–464. doi: 10.4193/Rhin20.600
37. Tay TR, Hew M. Comorbid "treatable traits" in difficult asthma: current evidence and clinical evaluation. *Allergy.* 2018;73:1369–1382. doi: 10.1111/all.13370
38. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA²LEN survey in Europe. *Allergy.* 2012;67(1):91–98. doi: 10.1111/j.1398-9995.2011.02709.x
39. Langdon C, Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. *J Asthma Allergy.* 2016;9:45–53. doi: 10.2147/JAA.S86251
40. Nenasheva N, Belevsky A, Kravchenko O, Avdeev S, Emel'yanov A, Kurbacheva O, Leschenko I. Late Breaking Abstract – Preliminary analysis of the data of patients with severe bronchial asthma included in the Russian National Register of Severe Asthma (RSAR). *Eur Respir J.* 2019;54(Suppl 63):PA4261. doi: 10.1183/13993003.congress-2019.pa4261
41. Maspero JF, Katelaris CH, Busse WW, Castro M, Corren J, Chipps BE, et al. Dupilumab efficacy in uncontrolled, moderate-to-severe asthma with self-reported chronic rhinosinusitis. *J Allergy Clin Immunol Pract.* 2020;8(2):527–539.e9. doi: 10.1016/j.jaip.2019.07.016
42. Busse W, Maspero J, Katelaris C, Saralaya D, Guillonneau S, Zhang B, et al. Dupilumab improves SNOT-22 scores in asthma patients with chronic rhinosinusitis or nasal polypsosis (CRS/NP) in LIBERTY ASTHMA QUEST. *Eur Respir J.* 2018;52(Suppl 62):PA1125. doi: 10.1183/13993003.congress-2018.pa1125
43. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis. *JAMA.* 2016;315(5):469–479. doi: 10.1001/jama.2015.19330
44. Bachert C, Hellings PW, Mullol J, Naclerio RM, Chao J, Amin N, et al. Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *J Allergy Clin Immunol Pract.* 2019;7(7):2447–2449. doi: 10.1016/j.jaip.2019.03.023
45. Bachert C, Jan JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet.* 2019;394(10209):1638–1650. doi: 10.1016/S0140-6736(19)31881-1

ЛИТЕРАТУРА

1. Agache I., Akdis C.A. Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases // *J Clin Invest.* 2019. Vol. 129. N 4. P. 1493–503. doi: 10.1172/JCI124611
2. Anderson G.P. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease // *Lancet.* 2008. Vol. 347. N 4. P.372(9643):1107–1119. doi: 10.1016/S0140-6736(08)61452-X
3. Lötvall J., Akdis C.A., Bacharier L.B., Bjermer L., Casale T.B., Custovic A., et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome // *J Allergy Clin Immunol.* 2011. Vol. 127. N 2. P. 355–360. doi: 10.1016/j.jaci.2010.11.037
4. Agache I., Akdis C., Jutel M., Virchow J.C. Untangling asthma phenotypes and endotypes // *Allergy.* 2012. Vol. 67. N 7. P. 835–846. doi: 10.1111/j.1398-9995.2012.02832.x
5. Agache I.O. From phenotypes to endotypes to asthma treatment // *Curr Opin Allergy Clin Immunol.* 2013. Vol. 13. N 3. P. 249–256. doi: 10.1097/ACI.0b013e32836093dd
6. Agache I., Akdis C.A. Endotypes of allergic diseases and asthma: an important step in building blocks for the future of precision medicine // *Allergol Int.* 2016. Vol. 65. N 3. P. 243–252. doi: 10.1016/j.alit.2016.04.011
7. Woodruff P.G., Modrek B., Choy D.F., Jia G., Abbas A.R., Ellwanger A., et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma // *Am J Respir Crit Care Med.* 2009. Vol. 180. N 8. P. 796. Corrected and republished from: *Am J Respir Crit Care Med.* 2009. Vol. 180. N 5. P. 388–395. doi: 10.1164/rccm.200903-0392OC
8. Bhakta N.R., Woodruff P.G. Human asthma phenotypes: from the clinic, to cytokines, and back again // *Immunol Rev.* 2011. Vol. 242. N 1. P. 220–232. doi: 10.1111/j.1600-065X.2011.01032.x
9. Ненашева Н.М. Т2-бронхиальная астма: характеристика эндотипа и биомаркеры // *Пульмонология.* 2019. Т. 29. № 2. С. 216–228. doi: 10.18093/0869-0189-2019-29-2-216-228
10. Agache I. Severe asthma phenotypes and endotypes // *Semin Immunol.* 2019. Vol. 46. P. 101301. doi: 10.1016/j.smim.2019.101301.
11. Agache I., Sugita K., Morita H., Akdis M., Akdis C.A. The complex type 2 endotype in allergy and asthma: from laboratory to bedside // *Curr Allergy Asthma Rep.* 2015. Vol. 15. N 6. P. 29. doi: 10.1007/s11882-015-0529-x

12. Agache I., Akdis C., Akdis M., Canonica G.W., Casale T., Chivato T., et al. EAACI Biologicals Guidelines – Recommendations for severe asthma // *Allergy*. 2020. P. 1–31. doi: 10.1111/all.14425
13. Сергеева Г.Р., Емельянов А.В., Коровина О.В., Знахуренко А.А., Лешенкова Е.В., Козырева Л.В., Асатиани Н. Тяжелая бронхиальная астма: характеристика пациентов в клинической практике // *Терапевтический архив*. 2015. Т. 87. № 12. С. 26–31. doi: 10.17116/terarkh2015871226-31
14. Schleich F., Brusselle G., Louis R., Vandenplas O., Michils A., Pilette C., et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR) // *Respir Med*. 2014. Vol. 108. N 12. P. 1723–1732. doi: 10.1016/j.rmed.2014.10.007
15. Shau D.E., Sousa A.R., Fowler S.J., Fleming L.J., Robers G., et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort // *Eur Respir J*. 2015. Vol. 46. N 5. P. 1308–1321. doi: 10.1183/13993003.00779-201
16. Gandhi N.A., Pirozzi G., Graham N.M. Commonality of the IL-4/IL-13 pathway in atopic diseases // *Expert Rev Clin Immunol*. 2017. Vol. 13. N 5. P. 425–437. doi: 10.1080/1744666X.2017.1298443
17. Weinstein S.F., Katial R., Jayawardena S., Pirozzi G., Staudinger H., Eckert L., et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma // *J Allergy Clin Immunol*. 2018. Vol. 142. N 1. P. 171–177.e1. doi: 10.1016/j.jaci.2017.11.051
18. Jonstam K., Swanson B.N., Mannent L.P., Cardell L.O., Tian N., Wang Y., et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis // *Allergy*. 2019. Vol. 74. N 4. P. 743–752. doi: 10.1111/all.13685
19. Furue K., Ito T., Tsuji G., Ulzii D., Vu Y.H., Kido-Nakahara M., et al. The IL-13-OVOL1-FLG axis in atopic dermatitis // *Immunology*. 2019. Vol. 158. N 4. P. 281–286. doi: 10.1111/imm.13120
20. Guttman-Yassky E., Bissonnette R., Ungar B., Suárez-Fariñas M., Ardeleanu M., Esaki H., et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis // *J Allergy Clin Immunol*. 2019. Vol. 143. P. 155–172. doi: 10.1016/j.jaci.2018.08.022
21. Markowitz J.E., Jobe L., Miller M., Frost C., Laney Z., Eke R. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated for 9 years // *J Pediatr Gastroenterol Nutr*. 2018. Vol. 66. N 6. P. 893–897. doi: 10.1097/MPG.0000000000001840
22. Hirano I., Dellon E.S., Hamilton J.D., Collins M.H., Peterson K., Chehade M., et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis // *Gastroenterology*. 2020. Vol. 158. N 1. P. 111–122.e10. doi: 10.1053/j.gastro.2019.09.042
23. Wynn T.A. IL-13 effector functions // *Annu Rev Immunol*. 2003. Vol. 21. P. 425–456. doi: 10.1146/annurev.immunol.21.120601.141142
24. Corren J. Role of interleukin-13 in asthma // *Curr Allergy Asthma Rep*. 2013. Vol. 13. N 5. P. 415–420. doi: 10.1007/s11882-013-0373-9
25. Paul W.E. History of interleukin-4 // *Cytokine*. 2015. Vol. 75. N 1. P. 3–7. doi: 10.1016/j.cyto.2015.01.038
26. Punnonen J., Aversa G., Cocks B.G., McKenzie A.N., Menon S., Zurawski G., et al. Interleukin-13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B-cells // *Proc Natl Acad Sci U S A*. 1993. Vol. 90. N 8. P. 3730–3734. doi: 10.1073/pnas.90.8.3730
27. Gascan H., Gauchat J.F., Roncarolo M.G., Yssel H., Spits H., de Vries J.E. Human B-cell clones can be induced to proliferate and to switch to IgE and IgG4 synthesis by interleukin 4 and a signal provided by activated $CD4^+$ T-cell clones // *J Exp Med*. 1991. Vol. 173. N 3. P. 747–750. doi: 10.1084/jem.173.3.747
28. Rosenberg H.F., Phipps S., Foster P.S. Eosinophil trafficking in allergy and asthma // *J Allergy Clin Immunol*. 2007. Vol. 119. N 6. P. 1303–1310. doi: 10.1016/j.jaci.2007.03.048
29. Le Floc'h A., Allinne J., Nagashima K., Scott G., Birchard D., Asrat S., et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation // *Allergy*. 2020. Vol. 75. N 5. P. 1188–1204. doi: 10.1111/all.14151
30. Castro M., Corren J., Pavord I.D., Maspero J., Wenzel S., Rabe K.F., et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma // *N Engl J Med*. 2018. Vol. 378. N 26. P. 2486–2496. doi: 10.1056/NEJMoa1804092.
31. Rabe K.F., Nair P., Brusselle G., Maspero J.F., Castro M., Sher L., et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma // *N Engl J Med*. 2018. Vol. 378. N 26. P. 2475–2485. doi: 10.1056/NEJMoa1804093
32. Manson M.L., Säfholm J., James A., Johnsson A.K., Bergman P., Al-Ameri M., et al. IL-13 and IL-4, but not IL-5 nor IL-17A, induce hyperresponsiveness in isolated human small airways // *J Allergy Clin Immunol*. 2020. Vol. 145. N 3. P. 808–817.e2. doi: 10.1016/j.jaci.2019.10.037
33. Gandhi N.A., Bennett B.L., Graham N.M., Pirozzi G., Stahl N., Vancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease // *Nat Rev Drug Discov*. 2016. Vol. 15. N 1. P. 35–50. doi: 10.1038/nrd4624
34. Bourdin A., Fabry-Vendrand C., Ostinelli J., Ait-Yahia M., Darnal E., Bouee S., et al. The burden of severe asthma in France: a case-control study using a medical claims database // *J Allergy Clin Immunol Pract*. 2019. Vol. 7. N 5. P. 1477–1487. doi: 10.1016/j.jaip.2018.12.029
35. Tiotiu A., Plavec D., Novakova S., Mihaicuta S., Novakova P., Labor M., et al. Current opinions for the management of asthma associated with ear, nose and throat comorbidities // *Eur Respir Rev*. 2018. Vol. 27. N 150. P. 180056. doi: 10.1183/16000617.0056-2018
36. Fokkens W.J., Lund V.J., Hopkins C., Hellings P.W., Kern R., Reitsma S., et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020 // *Rhinology*. 2020. N Suppl 29. 1–464. doi: 10.4193/Rhin20.600
37. Tay T.R., Hew M. Comorbid "treatable traits" in difficult asthma: current evidence and clinical evaluation // *Allergy*. 2018. Vol. 73. P. 1369–1382. doi: 10.1111/all.13370
38. Jarvis D., Newson R., Lotvall J., Hastan D., Tomassen P., Keil T., et al. Asthma in adults and its association with chronic rhinosinusitis: the GA²LEN survey in Europe // *Allergy*. 2012. Vol. 67. N 1. P. 91–98. doi: 10.1111/j.1398-9995.2011.02709.x

39. Langdon C., Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges // *J Asthma Allergy.* 2016. Vol. 9. P. 45–53. doi: 10.2147/JAA.S86251
40. Nenasheva N., Belevsky A., Kravchenko O., Avdeev S., Emel'yanov A., Kurbacheva O., Leschenko I. Late Breaking Abstract – Preliminary analysis of the data of patients with severe bronchial asthma included in the Russian National Register of Severe Asthma (RSAR) // *Eur Respir J.* 2019. Vol. 52. N Suppl 63. P. PA4261. doi: 10.1183/13993003.congress-2019.pa4261
41. Maspero J.F., Katelaris C.H., Busse W.W., Castro M., Corren J., Chipps B.E., et al. Dupilumab efficacy in uncontrolled, moderate-to-severe asthma with self-reported chronic rhinosinusitis // *J Allergy Clin Immunol Pract.* 2020. Vol. 8. N 2. P. 527–539.e9. doi: 10.1016/j.jaip.2019.07.016
42. Busse W., Maspero J., Katelaris C., Saralaya D., Guillonneau S., Zhang B., et al. Dupilumab improves SNOT-22 scores in asthma patients with chronic rhinosinusitis or nasal polypsosis (CRS/NP) in LIBERTY ASTHMA QUEST // *Eur Respir J.* 2018. Vol. 52. N Suppl 62. P. PA1125. doi: 10.1183/13993003.congress-2018.pa1125
43. Bachert C., Mannent L., Naclerio R.M., Mullol J., Ferguson B.J., Gevaert P., et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis // *JAMA.* 2016. Vol. 315. N 5. P. 469–479. doi: 10.1001/jama.2015.19330
44. Bachert C., Hellings P.W., Mullol J., Naclerio R.M., Chao J., Amin N., et al. Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma // *J Allergy Clin Immunol Pract.* 2019. Vol. 7. N 7. P. 2447–2449. doi: 10.1016/j.jaip.2019.03.023
45. Bachert C., Jan J.K., Desrosiers M., Hellings P.W., Amin N., Lee S.E., et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials // *Lancet.* 2019. Vol. 394. N 10209. P. 1638–1650. doi: 10.1016/S0140-6736(19)31881-1

Information about the author / Информация об авторе

Natalya M. Nenasheva, Doctor of Medical Sciences, Professor, Head of the Department of Allergology and Immunology, Federal State Budgetary Educational Institution of Russian Medical Academy of Continuous Professional Education. Address: 2/1, st. Barrikadnaya, building 1, 125993 Moscow, Russian Federation.
E-mail: 1444031@gmail.com
ORCID: http://orcid.org/0000-0002-3162-2510

Ненашева Наталья Михайловна, доктор медицинских наук, профессор, зав. кафедрой аллергологии и иммунологии Федерального государственного бюджетного образовательного учреждения дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации. Адрес: Российская Федерация, 125993, г. Москва, ул. Баррикадная, д. 2/1, стр. 1.
E-mail: 1444031@gmail.com
ORCID: http://orcid.org/0000-0002-3162-2510

Author contributions
Author prepared the manuscript and approved the submitted version before the publication.

Участие автора
Автор подготовил, прочел и одобрил финальную версию до публикации.

Funding information
The study had no sponsorship.

Информация об источниках финансирования
Исследование не имело спонсорской поддержки.

Conflict of interest
The author has no conflict of interest to disclose in relation to this article.

Конфликт интересов
Автор декларирует отсутствие конфликта интересов, связанных с публикацией настоящей статьи.