УДК 616.211-002.193-085.27:577.112:577.27:578.546.4
https://doi.org/10.20538/1682-0363-2025-4-59-67

Effect of Idelalisib on Cytokine Production by Blood Mononuclear Cells in Patients With Allergic Rhinitis

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ABSTRACT

Aim. To assess the ability of phosphatidylinositol 3-kinase δ inhibitor (idelalisib) to suppress cytokine production by peripheral blood mononuclear cells (PBMCs) of patients with allergic rhinitis.

Materials and methods. PBMCs of AR patients (n = 17) were incubated with idelalisib (0.5 μM) and recombinant proteins for induction of type 2 immune response (IR). Secretion of cytokines by PBMCs was determined by enzyme-linked immunosorbent assay. Intracellular production of cytokines in blood T-helper cells (CD4+) and cytotoxic (CD8+) T lymphocytes was analyzed by flow cytometry.

Results. Idelalisib significantly inhibited the secretion of interleukins (IL) 4, 8, 9, 13, 17A, interferon γ, and tumor necrosis factor α by PBMCs from patients with allergic rhinitis exposed to recombinant proteins (IL-2, IL-25, IL-33, and thymic stromal lymphopoietin) inducing type 2 IR. This drug also significantly suppressed the intracellular production of IL-4, IL-5, IL-13, and IL-17A by blood CD4+ and CD8+ T lymphocytes activated by type 2 IR.

Conclusion. The obtained data justify the need to conduct further clinical trials using idelalisib for the treatment of allergic rhinitis.

Keywords: allergic rhinitis, interleukin 25, interleukin 33, thymic stromal lymphopoietin, phosphatidylinositol 3-kinase δ, idelalisib

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The work was carried out as part of a joint assignment of the Belarusian Republican Foundation for Fundamental Research and the Russian Science Foundation (Contract No. M23RNF-021, state registration No. 20230281).

Conformity with the principles of ethics. The study was approved by the decision of the Biomedical Ethics Committee of Belarusian State Medical University (Minutes No. 1 dated August 31, 2023). Before blood sampling, all subjects gave a written voluntary consent to participate in the study.

For citation: Makarevich V.V., Kadushkin A.G., Tahanovich A.D., Mironova T.V., Kolesnikova T.S., Nazarenko E.M., Levandovskaya O.V., Shilovskiy I.P., Khaitov M.R., Dziadzichkina O.V. Effect of Idelalisib on

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cytokine production by blood mononuclear cells in patients with allergic rhinitis. *Bulletin of Siberian Medicine.* 2025;24(4):59–67. https://doi.org/10.20538/1682-0363-2025-4-59-67.

Влияние иделалисиба на продукцию цитокинов мононуклеарными клетками крови пациентов с аллергическим ринитом

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РЕЗЮМЕ

Цель. Оценить способность ингибитора фосфатидилинозитол-3-киназы δ (иделалисиба) подавлять продукцию цитокинов мононуклеарными клетками (МН-клетками) крови пациентов с аллергическим ринитом.

Материалы и методы. Мононуклеарные клетки пациентов с аллергическим ринитом (n = 17) инкубировали с иделалисибом (0,5 мкМ) и рекомбинантными белками для индукции 2-го типа иммунного ответа (ИО). Секрецию цитокинов МН-клетками определяли методом иммуноферментного анализа. Внутриклеточную продукцию цитокинов в Т-хелперах (CD4+) и цитотоксических (CD8+) Т-лимфоцитах крови анализировали методом проточной цитометрии.

Результаты. Иделалисиб существенно супрессировал секрецию интерлейкинов (ИЛ) 4, 8, 9, 13, 17A, интерферона γ, фактора некроза опухоли α МН-клетками крови пациентов с аллергическим ринитом, подвергшимся воздействию рекомбинантных белков (ИЛ-2, ИЛ-25, ИЛ-33, тимического стромального лимфопоэтина), индуцирующих ИО 2-го типа. Данный препарат также значительно подавлял внутриклеточную продукцию ИЛ-4, ИЛ-5, ИЛ-13, ИЛ-17A CD4+ и CD8+ Т-лимфоцитами крови, активированными по ИО 2-го типа.

Заключение. Полученные данные обосновывают необходимость интенсификации клинических исследований с применением иделалисиба для лечения аллергического ринита.

Ключевые слова: аллергический ринит, интерлейкин 25, интерлейкин 33, тимический стромальный лимфопоэтин, фосфатидилинозитол-3-киназа δ, иделалисиб

Конфликт интересов. Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена в рамках совместного задания Белорусского республиканского фонда фундаментальных исследований и Российского научного фонда (договор № М23РНФ-021, государственная регистрация № 20230281).

Соответствие принципам этики. Перед забором крови все испытуемые дали письменное добровольное согласие на участие в исследовании. Исследование одобрено комитетом по биомедицинской этике БГМУ (протокол № 1 от 31.08.2023).

Для цитирования: Макаревич В.В., Кадушкин А.Г., Таганович А.Д., Миронова Т.В., Колесникова Т.С., Назаренко Е.М., Левандовская О.В., Шиловский И.П., Хаитов М.Р., Дядичкина О.В. Влияние иделалисиба на продукцию цитокинов мононуклеарными клетками крови пациентов с аллергическим ринитом. *Бюллетень сибирской медицины.* 2025;24(4):59–67. https://doi.org/10.20538/1682-0363-2025-4-59-67.

INTRODUCTION

Allergic rhinitis affects 10–30% of the population in different regions worldwide and is characterized by inflammation of the nasal mucosa, which forms as a result of immunoglobulin (Ig) E-mediated hypersensitivity reaction to various allergens. The use of currently available treatment methods does not lead to the complete relief of the allergic rhinitis symptoms [1]. In addition, approximately 11% of patients, when treating this disease, experience side effects of drugs [2]. Therefore, research aimed at finding alternative approaches to the treatment of allergic rhinitis remains relevant.

When exposed to allergens, epithelial cells of the nasal mucosa secrete cytokines, such as thymic stromal lymphopoietin (TSLP), interleukins (IL) 25 and 33, which upon entering the systemic circulation activate dendritic cells, type 2 innate lymphoid cells (ILC2 cells), and type 2 T-helper cells (Th2-lymphocytes). These cells, in turn, produce IL-4, IL-5, IL-13, and other mediators, which leads to the attraction of eosinophils to the nasal mucosa, their activation, and degranulation, synthesis of IgE by B lymphocytes, and mucus hyperproduction by the epithelium [3].

It was proposed that phosphatidylinositol 3-kinase (PI3K) δ may play a central role in the production of the above-mentioned cytokines. The results of experimental studies indicate that the signaling pathways mediated by this enzyme are involved in the inflammatory process in allergic rhinitis [4, 5]. In this case, the use of a PI3Kδ inhibitor in combination with a serine proteinase inhibitor 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride led to weakening of the type 2 immune response (IR) in mice sensitized to cockroach allergens [6]. Results of phase I clinical trial of idelalisib (a PI3Kδ inhibitor) for the treatment of allergic rhinitis demonstrated its ability to reduce the severity of disease symptoms, CCL17 and CCL22 concentration in blood plasma, and the percentage of *ex vivo* activated (using grass pollen allergen) blood basophils [4]. However, the ability of PI3Kδ inhibitors to suppress the production of proinflammatory cytokines by blood cells in patients with allergic rhinitis has not been previously studied.

Thus, the aim of this study was to evaluate the ability of idelalisib (a PI3Kδ inhibitor) to suppress the production of proinflammatory cytokines by peripheral blood mononuclear cells (PBMCs) of patients with allergic rhinitis.

MATERIALS AND METHODS

Patient Characteristics

The study involved 17 patients aged 18 to 23 years who were diagnosed with allergic rhinitis at least 1 year before inclusion in the study (Table). The overwhelming majority (10; 58.8%) of patients suffered from perennial allergic rhinitis, while a smaller proportion (7; 41.2%) of patients suffered from the seasonal form of allergic rhinitis.

Table

Characteristics of Patients with Allergic Rhinitis who Participated in the Study

Indicator		Patients, $n = 17$
Age, years, $M \pm m$		20.0 ± 0.3
Sex, male/female		8/9
BMI, kg/m², $M \pm m$		21.5 ± 0.7
Form of allergic rhinitis (PAR/SAR)		10/7
Disease duration, years, $M \pm m$		12.5 ± 1.1
SNOT-22 questionnaire score, $M \pm m$		42.9 ± 4.4
TNSS questionnaire score, $M \pm m$		7.3 ± 0.4
Drugs used, *n* (%)	Oral antihistamines	15 (88.24%)
	Endonasal antihistamines	5 (29.41%)
	Intranasal corticosteroids	6 (35.29%)
	Leukotriene receptor antagonists	1 (5.88%)
	Endonasal saline solution	6 (35.29%)
	Decongestants	4 (23.53%)

Note. BMI – body mass index; PAR – perennial allergic rhinitis; SAR – seasonal allergic rhinitis; TNSS – total nasal symptom score; SNOT-22 (sino-nasal outcome test) – a test for assessing the quality of life and therapeutic results of treatment of patients with diseases of the nose and paranasal sinuses.

We excluded from the study patients with anatomical abnormalities of the nasal septum, with concomitant diseases (asthma, tuberculosis, diabetes mellitus, chronic rhinosinusitis, arterial hypertension, cardiovascular, and oncological diseases), other concomitant diseases requiring medication; immunodeficiency states, including those caused by HIV, or blood coagulation disorders; those who underwent a course of allergen-specific immunotherapy; had infectious diseases of the respiratory tract or gastrointestinal tract or took antibiotics during the last 6 weeks before enrollment in the study, and pregnant women. Patients refrained 3 days before the study from taking antihistamines, and 2 weeks before the study from taking oral and nasal corticosteroids. The patients refrained from taking antihistamines for three days before the study. They refrained from oral and nasal corticosteroids for two weeks before the study and from dietary supplements for one week before inclusion in the study.

Isolation and Incubation of Peripheral Blood Mononuclear Cells

PBMCs were isolated from heparinized blood of patients by 1.077 density gradient centrifugation using Lymphosep solution (Biowest, France). Cells were resuspended at a concentration of 1×10^6/ml in RPMI 1640 culture medium (Capricorn Scientific, Ebsdorfergrund, Germany) supplemented with 10% fetal bovine serum (FBS, Capricorn Scientific, collected in South America), 2 mM glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin (Capricorn Scientific).

Then 2×10^5 PBMCs were placed in wells of a 96-well plate and cultured in the presence or absence of 0.5 μM idelalisib (p110δ PI3K inhibitor) (Cayman Chemicals, USA). Subsequently, to induce type 2 IR, the cells were activated by adding recombinant proteins produced by Biolegend (USA): IL-2 (20 U/ml), IL-25 (50 ng/ml), IL-33 (50 ng/ml), and TSLP (50 ng/ml). After three days of cell incubation, the supernatants were collected and stored at –80°C. The concentrations of IL-4, IL-6, IL-8, tumor necrosis factor (TNF) α, interferon (IFN) γ (Vector Best, Russian Federation), IL-9, IL-13, and IL-17A (Biolegend, USA) were determined in the supernatants using enzyme-linked immunosorbent assay according to the manufacturer's instructions.

Evaluation of Intracellular Cytokine Production by Blood T Lymphocytes

PBMCs were adjusted to 0.8×10^6 cells per well in the 24-well plate and cultured in the presence or absence of idelalisib and recombinant proteins (in the similar concentrations as described above). To accumulate cytokines inside the cell (to prevent their secretion outside the cell), 10 μg/ml brefeldin A (Biolegend, USA) was added before the last 16 hours of incubation. The total incubation time of the cells with recombinant proteins was three days.

Next, 0.4×10^6 cells were transferred into new tubes and washed twice with wash buffer (phosphate-buffered saline containing FBS and sodium azide (Biolegend, USA). A cocktail of monoclonal antibodies to surface antigens (CD45, CD3, CD4, and CD8, Biolegend, USA; Exbio, Prague, Czech Republic) was added, and the cells were incubated for 20 min in the dark at room temperature. The cells were then washed with wash buffer (centrifugation conditions: 500g, 5 min). After fixation of leukocytes (using fixation buffer, Biolegend, USA), the cells were permeabilized using permeabilization buffer (Biolegend, USA), and monoclonal antibodies to IL-4 APC, IL-5 PE, IL-13 APC, and IL-17A PE (Biolegend, USA; BD Biosciences, USA) were added for 20 minutes in the dark at room temperature. In our experiments, we also used unstimulated and isotype controls to ensure proper fluorescence compensation and confirm antibody specificity.

Next, 3 ml of wash buffer was added, and the tubes were centrifuged at 500g for 5 minutes. After removing the supernatant, 500 μl of 1% paraformaldehyde in phosphate-buffered saline was added to the tubes, and the cells were analyzed no later than 24 hours on a CytoFLEX flow cytometer (Beckman Coulter). The results of the study were further evaluated using CytExpert 2.3 software (Beckman Coulter). Samples were analyzed by gating lymphocytes using CD45 antibody and side scatter signal. T-helper cells were identified as $CD45^+CD3^+CD4^+$ events, and cytotoxic T lymphocytes were defined as $CD45^+CD3^+CD8^+$ cells. Then, the intracellular synthesis of IL-4, IL-5, IL-13, and IL-17A by T-helper cells and cytotoxic T lymphocytes was analyzed.

Statistical Data Processing

Statistical data processing was performed using the GraphPad Prism 7 statistical data analysis package (GraphPad Software, USA). The results of the study are presented as the mean and the standard error of the mean $M \pm m$ from the total number of observations with normal data distribution, which was confirmed by constructing distribution histograms and applying the Shapiro–Wilk test. The study results were assessed using the one-way analysis of variance (ANOVA) method with post-hoc pairwise comparison of values using the Tukey test. For all types of statistical analysis, the critical value of the significance level was taken as equal to 5%.

RESULTS

The results of the study showed an increase in the secretion of IL-4, IL-8, IL-9, IL-13, IL-17A, TNFα, and IFNγ upon induction of type 2 IR (by adding IL-2, IL-25, IL-33, and TSLP to the culture medium) (Fig. 1). The analysis of intracellular production of cytokines by blood $CD4^+$ and $CD8^+$ T lymphocytes demonstrated a rise in the synthesis of IL-4, IL-5, and IL-13 by both subpopulations of T lymphocytes, as well as IL-17A by blood cytotoxic T lymphocytes of patients with allergic rhinitis upon the influence of IL-2, IL-25, IL-33, and TSLP combination (compared to cells cultured without these recombinant proteins) (Fig. 2).

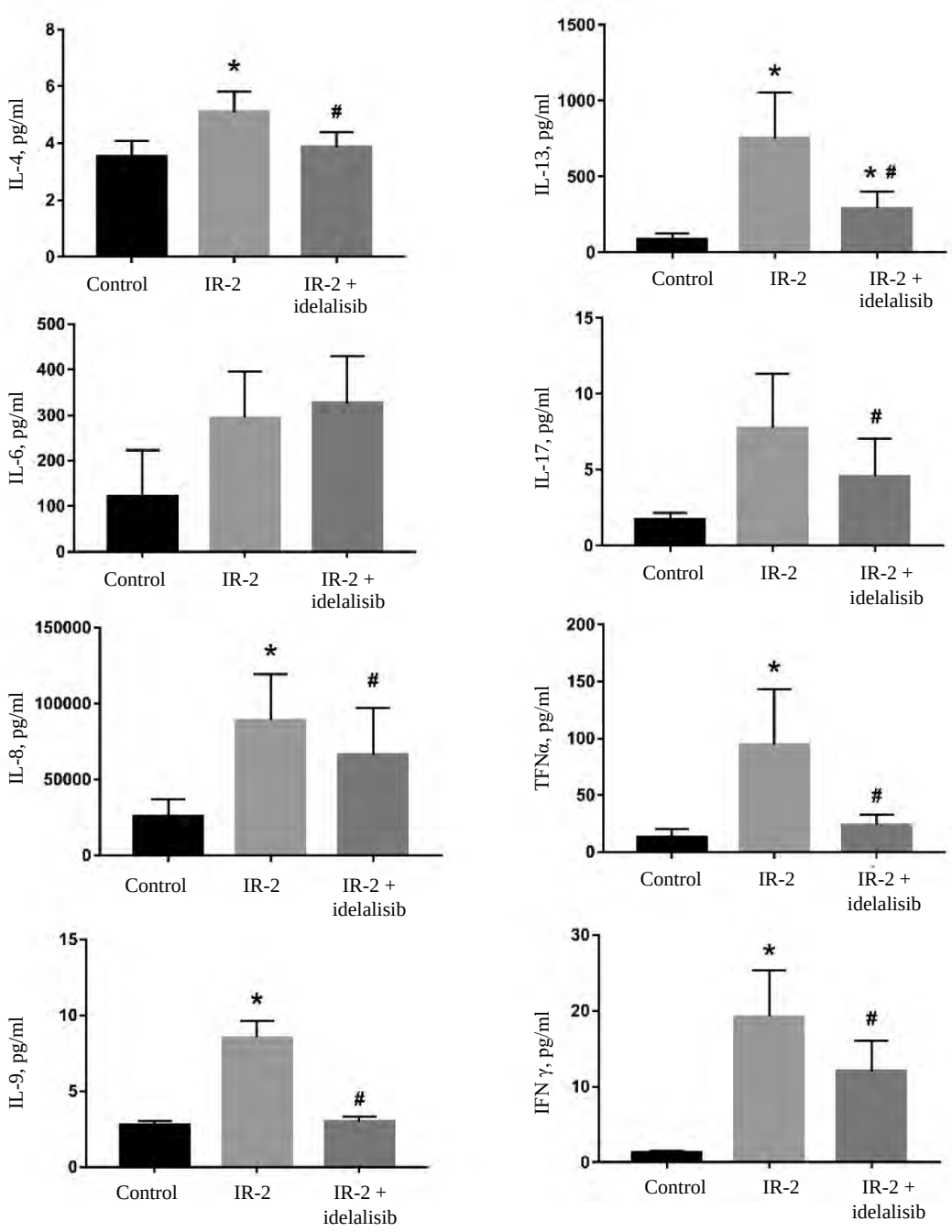

Fig. 1. Effect of idelalisib on cytokine (IL-4, IL-6, IL-8, IL-9, IL-13, IL-17A, TNFα, and IFNγ)production by peripheral blood mononuclear cells (PBMCs) in patients with allergic rhinitis; $M \pm m$, $n = 6$, $p < 0.05$; * compared with control (cells incubated in the absence of recombinant proteins); # compared with cells activated by type 2 immune response (without idelalisib). PBMCs were incubated with idelalisib (0.5 μM) and recombinant proteins to induce type 2 immune response (IR-2). Secretion of cytokines was determined by enzyme-linked immunosorbent assay

Next, we assessed the ability of the p110δ phosphatidylinositol 3-kinase inhibitor to affect the production of inflammatory mediators by PBMCs of patients with allergic rhinitis (Fig. 1, 2).

It turned out that idelalisib is able to suppress the secretion of IL-4, IL-8, IL-9, IL-13, IL-17A, TNFα, and IFNγ by PBMCs upon induction of type 2 IR. In addition, upon stimulation of type 2 IR, idelalisib inhibited the production of IL-4, IL-5, IL-13, and IL-17A by blood T-helper cells and cytotoxic T lymphocytes of patients with allergic rhinitis.

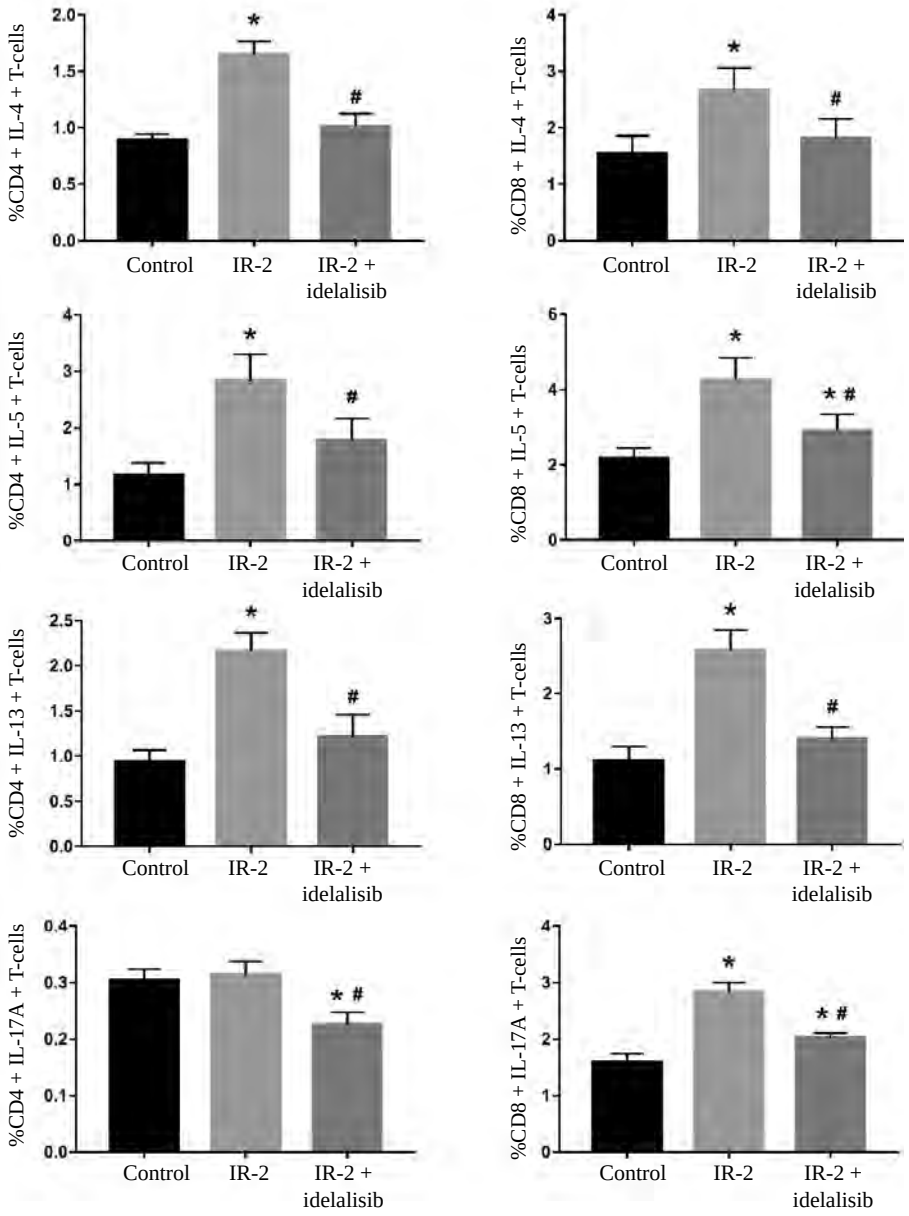

Fig. 2. Effect of idelalisib on intracellular cytokine production (IL-4, IL-5, IL-13 and IL-17A) by blood T-helper cells ($CD4^+$) and cytotoxic T lymphocytes ($CD8^+$)in patients with allergic rhinitis: $M \pm m$, $n = 5–6$, $p < 0.05$; * compared with control (cells incubated in the absence of recombinant proteins); # compared with cells activated by type 2 immune response (without idelalisib). Peripheral blood cells were incubated with idelalisib (0.5 μM) and recombinant proteins to induce type 2 immune response (IR-2). The level of IL-4 synthesis by T lymphocytes as determined by flow cytometry

DISCUSSION

PI3K are a group of enzymes involved in signal transduction into the cell through the production of secondary messengers. Under the action of PI3K, phosphatidylinositol-3,4,5-triphosphate is formed, which phosphorylates (activates) Akt kinase. The latter activates many effector molecules that control cell growth, metabolism, viability, and chemotaxis. In leukocyte cells, the p110δ PI3K isoform is predominantly found [7], which is involved in the activation and differentiation of T lymphocytes, their migration to the site of inflammation, and production of cytokines [8]. The expression of phosphoribosomal protein S6, which reflects PI3K activity, has been found to be increased in bronchial epithelial cells of patients with asthma after exposure to an allergen, indicating the importance of PI3K in allergic diseases [9].

Allergic rhinitis is a disease characterized by the formation of type 2 IR. Previously, it has been

shown that such an IR develops under the influence of IL-2, IL-25, IL-33, and TSLP on epithelial and immune cells and is accompanied by an increase in the concentration of IL-4, IL-5, IL-9, and IL-13 in the blood serum and nasal washes of patients with allergic rhinitis [10]. In the present study, idelalisib (p110δ PI3K inhibitor) reduced the production of IL-4, IL-9, and IL-13 by PBMCs and suppressed the intracellular synthesis of IL-4, IL-5, and IL-13 by blood T-helper cells and cytotoxic T lymphocytes of patients with allergic rhinitis upon the induction of type 2 IR. The data obtained demonstrate the ability of idelalisib to significantly inhibit the inflammatory response in patients with allergic rhinitis.

In our study, we also assessed the production of IL-8 and IL-17A in response to idelalisib action and stimulation of PBMCs by type 2 IR. IL-17A belongs to the group of cytokines produced by type 17 T-helper cells, while IL-8 is produced by numerous cell populations, including alveolar macrophages, T lymphocytes, mast cells, fibroblasts, epithelial and endothelial cells, platelets, and neutrophils [11, 12]. It is noteworthy that IL-17A can increase IL-8 expression in epithelial and endothelial cells of patients with allergic rhinitis, thereby enhancing neutrophil migration to the site of allergic inflammation [13, 14]. It is known that IL-8 and IL-17A concentration is increased in the blood serum of patients with allergic rhinitis compared with healthy individuals [11, 15]. Moreover, endonasal provocation test with an allergen in patients with allergic rhinitis led to an increase in IL-8 and IL-17A level in nasal lavage [16, 17]. Our experiments demonstrated the inhibitory effect of idelalisib on the secretion of IL-8 and IL-17A by PBMCs of patients with allergic rhinitis upon stimulation of type 2 IR. In addition, idelalisib reduced the production of IL-17A by blood $CD4^+$ and $CD8^+$ T lymphocytes of patients with allergic rhinitis. These results suggest the ability of idelalisib (due to the suppression of IL-8 and IL-17A) to inhibit neutrophil chemotaxis in patients with allergic rhinitis.

TNFα induces the production of antigen-specific IgE, Th2 cytokines and chemokines, as well as adhesion molecules involved in attracting eosinophils to the site of allergic inflammation. Moreover, TNFα deficiency slows down the development of allergic rhinitis [18]. An association between the polymorphic variant of the rs769178 locus of the *TNFα* gene, haplotypes (C-G-A-T and C-G-C-T) of the *TNFα* gene, and an increased risk of allergic rhinitis has been reported [19]. In a mouse model of allergic rhinitis, the TNFα inhibitor infliximab demonstrated antiallergic action by reducing the production of IL-4 and IgE, expression of adhesion molecules (E-selectin), and migration of eosinophils into the nasal mucosa [20]. In this study, suppression of TNFα production by PBMCs of patients with allergic rhinitis was achieved by adding idelalisib to the culture medium, which indicates the ability of this drug to effectively reduce the expression and synthesis of TNFα.

Another proinflammatory mediator whose production was assessed in this study is IFNγ, a key Th1 cytokine (Fig. 1). It is known for its ability to induce the production of chemokines CXCL9, CXCL10, CXCL11, which attract T lymphocytes expressing CXCR3 receptors to the site of inflammation. An increase in IFNγ production by blood $CD4^+$ T cells of patients with allergic rhinitis upon contact with allergens has been demonstrated [21], along with an increase in CXCL9 and CXCL10 concentration in nasal washes of patients with allergic rhinitis 30 minutes after exposure to the allergen [22], which indicates the importance of IFNγ and IFNγ-induced chemokines in the allergic inflammation. In our work, in response to stimulation of PBMCs of patients with allergic rhinitis according to type 2 IR, IFNγ production was increased. Addition of idelalisib to the culture medium resulted in the decreased synthesis of this cytokine. Thus, in the present study, under type 2 IR conditions, idelalisib suppressed the synthesis of Th2 cytokines, as well as Th1 and Th17 cytokines.

To date, only a single phase I clinical trial has been conducted on a small sample of patients evaluating the use of idelalisib for the treatment of allergic rhinitis, demonstrating its good tolerability, clinical efficacy, and ability to reduce the level of several inflammatory mediators in the blood of patients [4]. The data obtained in this study confirm high anti-inflammatory efficacy of this drug and indicate the need for further clinical trials using idelalisib for the treatment of patients with allergic rhinitis.

CONCLUSION

The results of the study showed that idelalisib (an inhibitor of the p110δ isoform of PI3K) can significantly suppress the secretion of cytokines (IL-4, IL-8, IL-9, IL-13, IL-17A, TNFα, and IFNγ) by PBMCs of patients with allergic rhinitis exposed to recombinant proteins (IL-2, IL-25, IL-33, and TSLP) that induce type 2 IR. This drug also significantly suppressed the intracellular production of IL-4, IL-5,

IL-13, and IL-17A in blood cytotoxic T lymphocytes and T-helper cells activated by type 2 IR. The data obtained justify the need to intensify clinical trials using idelalisib for the treatment of allergic rhinitis.

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Makarevich V.V. – conducting biochemical studies, interpreting data, drafting of the manuscript. Kadushkin A.G. – conception and design, drafting of the manuscript, final approval of the manuscript for publication. Tahanovich A.D., Shilovskiy I.P., Khaitov M.R. – conception and design. Mironova T.V., Kolesnikova T.S., Nazarenko E.M., Levandovskaya O.V. – conducting biochemical studies, data interpretation. Dziadzichkina O.V. – statistical data processing.

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Received on July 31, 2025;
approved after peer review on August, 2025;
accepted on September 9, 2025