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Possibilities of Control of IgE-Associated Respiratory Diseases in Pediatric Practice. Clinical Case

KO Avetisyan[1]* and SG Makarova[1,2]

1National Research Center for Children's Health, Russian Federation

2Moscow State University. M.V. Lomonosov, Russian Federation

***Corresponding author:** Karine Onikovna Avetisyan, Allergist-Immunologist, Junior Researcher, National Medical Research Center for Children's Health, Moscow, Russia

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ABSTRACT

Bronchial asthma (BA) is a heterogeneous disease characterized by chronic inflammation of the airways. Severe asthma occurs in all age groups and represents a clinically and etiologically heterogeneous group, accounting for about 5–10% of patients with asthma. Achieving control over the disease is the main and important task of treating bronchial asthma in all its forms. Despite existing clinical guidelines for the treatment of asthma, studies show that approximately 50% of patients remain poorly controlled. This problem is also relevant in adolescence, especially in severe forms of the disease. Adolescent children with uncontrolled asthma have a poor quality of life, many absences from school due to frequent exacerbations or asthma symptoms, do not leave the house, lead a passive lifestyle, may have depression and other psychological and social disorders. Modern methods of asthma therapy, based on the molecular mechanisms and pathogenesis of the disease, allow solving the issues of providing effective medical care to patients with uncontrolled moderate and severe asthma. They allow you to achieve control over the symptoms of the disease, minimize the risks of future exacerbations. This article presents a clinical example of a teenager with severe uncontrolled asthma, with concomitant allergic persistent rhinitis and hay fever. Anti-IgE biological therapy with omalizumab was prescribed. In a short period of therapy, control of asthma symptoms is achieved. The frequency of asthma exacerbation was reduced, the use of systemic corticosteroids (SCS) until their complete cessation, the use of short-acting inhaled β2-agonists (SABA) was reduced to a minimum, and the dosage of inhaled hormones (IGCS) was reduced. As a result, the quality of life of a teenager is improved, the levels of his physical and daily activity and socialization are increased.

Keywords: Asthma Control; Adolescence; Allergic Rhinitis; IgE; Eosinophilia; Spirometry; Biologic Therapy; Severe Asthma

Abbreviations: BA: Bronchial Asthma; SCS: Systemic Corticosteroids; SABA: Short-Acting Inhaled β2-Agonists; AR: Allergic Rhinitis, AD: Atopic Dermatitis

Introduction

Bronchial asthma (BA) is one of the most common multifactorial chronic diseases in childhood [1]. Currently, more than 300 million people in the world suffer from AD. The prevalence of this pathology among adolescents reaches approximately 13% [2,3]. The classic manifestations of asthma are the presence of expiratory wheezing, shortness of breath, cough, or a "feeling of heaviness" in the chest area [4]. Achieving disease control and reducing the risk of future exacerbations is the main goal of asthma treatment. Currently, there is evidence that up to 59% of patients do not achieve full control of asthma [5]. It should be noted that in childhood, in most cases, BA is the final stage of the atopic march, when atopic dermatitis (AD) first starts in one patient, then symptoms of allergic rhinitis (AR) are observed, and subsequently bronchial asthma develops. According to the mechanism, this process is heterogeneous and it involves both internal, including genetic factors, and modifying risk factors of the external environment: microbes, irritants, allergens, living conditions of the child, environmental factors, geographical and ethnic characteristics, smoking, and others [6,7]. AR is considered as a risk factor for the development of bronchial asthma, on the other hand, its uncontrolled course leads to a decrease in control over asthma symptoms. Thus, AR is an independent predictor of adverse outcomes in AD. Perhaps this relationship is due to the concept of the unity and integrity of the respiratory system and common pathogenetic immune mechanisms of AR and AD. For this reason, when organizing AD therapy, much attention is paid to the treatment and control of AR.

Epidemiological studies show that 0.5% of children in the general population and 4.5% of children with asthma suffer from severe asthma [8,9]. The treatment of severe asthma is currently a global problem [10]. Factors contributing to the lack of control of asthma include: failure to control exposure to environmental triggers (allergens, irritants, germs, smoking, and others), misuse of inhalers, poor adherence to therapy, presence of uncontrolled comorbidities, psychosocial and socioeconomic factors, genetic factors, phenotypic features [11]. Severe asthma is currently defined as the need for (not just prescription or use of) high-intensity treatment after appropriate treatment of modifiable factors and comorbidities [12]. Poor adherence is not uncommon as a result of disease progression. When treatment does not help, the patient will lose the desire and motivation to follow all the doctor's recommendations. This often happens in teenagers. They lose trust in the doctor, mistakenly conclude that they have an incurable disease, and further isolate themselves from their peers and an active society. A vicious circle is formed. Uncontrolled asthma increases the risk of subsequent exacerbations [13,14]. This leads to the fear of death from suffocation in patients and their parents, various cognitive impairments in patients [15]. Adolescent children with uncontrolled asthma have a poor quality of life [16] and mental health problems [17].

Against the background of an uncontrolled course of the disease, patients often and uncontrollably use inhaled SABA, which further contributes to the deterioration of the severity of the disease, increases the risk for future exacerbations [18]. And all of the above can lead to unfair disability of patients. Such an outcome of asthma is not acceptable in childhood. To select an effective therapy strategy for patients with uncontrolled asthma with moderate and severe severity, it is extremely important to determine the endotypes and phenotypes of asthma. In childhood, AD in most cases has an atopic phenotype [19]. Atopy is associated with a pathological immune response to the entry of allergens into the body in the form of hyperproduction of specific immunoglobulins E (IgE). The atopic phenotype of asthma is the more common phenotype for T2 endotype asthma. Determination of phenotypic biomarkers provides a strategy for targeted targeted therapy [20]. In clinical practice, therapies for severe asthma that target phenotypic and causative cytokines or their receptors, and hence the pathogenetic mechanisms of the disease, are increasingly showing their effectiveness. Anti - IgE therapy is such an example of the treatment of severe atopic AD in adolescents and solves the difficult issues associated with achieving disease control [21]. For this reason, biological therapy has been widely introduced into clinical practice, and in daily practice we often rejoice in the success of pathogenetic therapy together with our patients and their parents. One such clinical example is presented below in the article.

Purpose Demonstration of a Clinical Case

To demonstrate the tactics and strategy of therapy for a teenager with severe uncontrolled asthma, to show the therapeutic value and effectiveness of pathogenetic therapy with a biological drug - omalizumab in real clinical practice.

Description of the Clinical Case

Teenager M., 17 years old. At the age of 5 he was diagnosed with allergic rhinitis, at 7 years of hay fever, at 9 years of age he had bronchial asthma. An allergological blood test using the ImmunoCap method revealed a high sensitization to birch pollen and cat epithelium. In Russia, one of the highly allergenic pollen allergens is birch pollen, and a cat is also a frequent aeroallergen. Exacerbation of pollinosis was observed in the flowering season of trees (spring) in the form of allergic rhinitis, conjunctivitis, then with asthma attacks. Several times for the relief of severe asthma attacks, he was hospitalized and received SCS treatment in a hospital. He was observed by an allergist - an immunologist at the place of residence. At the age of 12, he was on basic therapy - fluticasone propionate 1000 mcg / salmeterol 200 mcg per day in a multidisk device and montelukast 5 mg per day. For relief of symptoms, SABA (salbutamol) was prescribed in a metered-dose aerosol device. His therapy was optimized to control allergic rhinitis with daily intranasal mometasone furoate, saline rinses, antihistamines. Also, elimination therapy was carried out with the restriction of aeroallergens. Against the background of the therapy, it was not possible to achieve control over the symptoms of asthma. Despite treatment, he had daily symptoms of asthma: paroxysmal cough, wheezing, shortness of breath, choking, chest discomfort, fatigue, sleep disturbance. He required frequent and daily inhalations of salbutamol.

He missed school a lot due to a serious illness and frequent exacerbations. His asthma was always exacerbated during ARVI and often required SCS for relief, he was hospitalized 2-3 times a year and received intensive care. Frequent triggers were viral infections, physical activity, stress, aeroallergens. Due to uncontrolled asthma, the teenager was released from physical education, and physical activity was completely excluded. He spent more time at home. The allergist tried to add a second IGCS molecule - cyclosonide 160mcg 1 time in the evening. But also, without result. At the age of 12, he was hospitalized in a specialized institution: the Scientific Center for Children's Health to decide on the further therapy of a teenager. Diagnosis at admission: Bronchial asthma, atopic form, persistent course, severe severity, uncontrolled. Concomitant disease: allergic persistent rhinitis, severe course, not controlled; pollinosis - remission. Upon admission to the department:

- The result of the BA control test (ACT) - 12 points.
- The results of spirometry at admission: Decreased ventilation function of the lungs by obstructive type, FEV1 74% of the norm, bronchodilator test is strongly positive. The increase in FEV1 amounted to 550 ml.
- Eosinophilia in peripheral blood - 6.1% or 400 cells/μl.
- Total IgE 225 IU/ml.

A decision was made to initiate biological therapy - monoclonal antibodies - anti- IgE therapy with omalizumab - 225 mg, subcutaneous injections with an interval of 1 time in 4 weeks.

Clinical Monitoring Against the Background of Pathogenetic Therapy and Results

Positive dynamics was assessed from the 2nd month of therapy, and already 6 months after the appointment of biological therapy, the teenager and his parents notice a significant improvement in their asthma control.

- The need for SABA is minimal, no more than 1-2 times a month and only after increased physical activity. There are no nocturnal symptoms, and the quality of sleep does not suffer. The result of AST increases exponentially to 21-22 points.
- Improved spirometry. Sustained increase in FEV1 up to 90-95%. The increase in FEV1 on the bronchodilatory test gradually decreased. A year after the start of biological therapy, the bronchodilatory test became negative and this result was maintained during further observation up to 18 years Figure 1. shows the monitoring of the FEV1 increase during the bronchodilation test with salbutamol 200mcg.
- Against the background of therapy, exacerbations of BA ceased and were not observed, including during respiratory infections. The frequency of respiratory infections decreased and SCS was not applied.
- There was a marked improvement in nasal breathing and an improvement in quality of life associated with AR symptoms.
- Pollinosis proceeded in a mild form, and exacerbation of BA was not observed during the tree flowering season.
- Decreased eosinophils in peripheral blood. We obtained a statistically significant decrease in the absolute and relative numbers of eosinophils in peripheral blood during the entire observation period against the background of biological therapy. Observation data for 2 years against the background of biological therapy are presented in Figure 2. The graph shows that eosinophils are in the normal range against the background of therapy. In the future, high numbers were not observed.

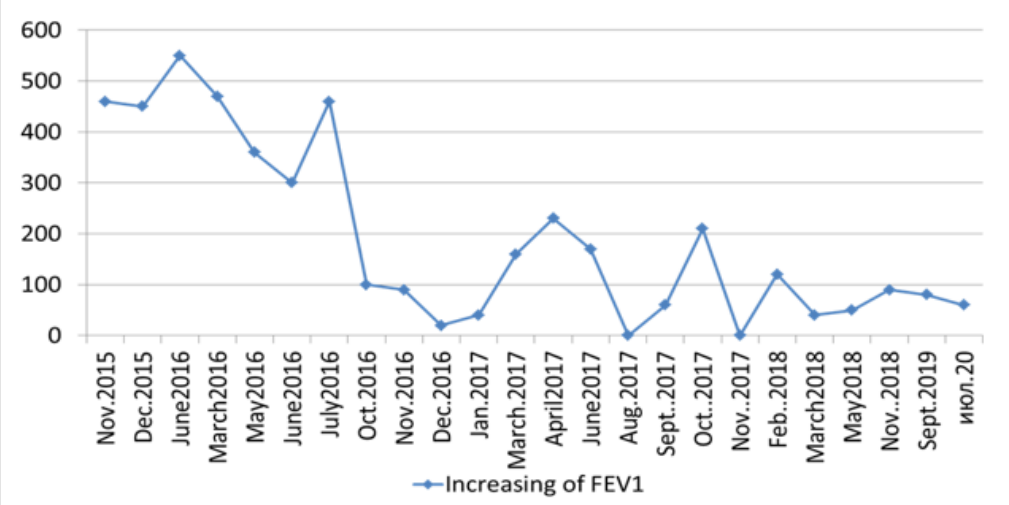

Figure 1: Monitoring of bronchodilation test evaluation.

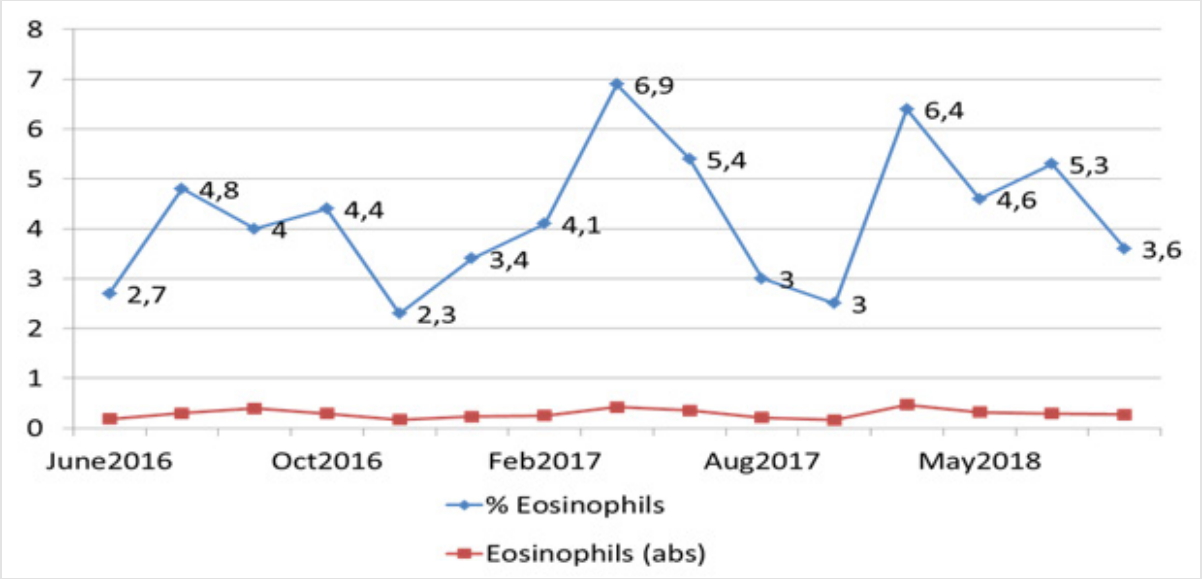

Figure 2: Dynamics of blood eosinophilia 2016-2020.

- The graphs show a decrease in eosinophilia (Figure 1) and an increase in FEV1 (Figure 2) during therapy.We saw a correlation between these two important indicators.

- The level of physical and social activity of a teenager is increased, his psycho-emotional state is improved. He and his parents are no longer afraid of asthma attacks. They are no longer haunted by the fear of suffocation and death. The teenager stopped hiding from society, from peers. By the way, he had an improvement in the condition of the skin in relation to acne. He began to attend school well, physical education classes. He had activity and interests in life.

- Anti-IgE therapy was continued until May 2021, when the teenager turned 18 and was referred to an adult allergist for further therapy.

Findings

The demonstration of a clinical example clearly demonstrates the possibilities of controlling IgE-associated severe respiratory diseases in pediatric practice. Pathogenetic Anti-IgE therapy with monoclinic antibodies to IgE in a teenager with severe uncontrolled atopic bronchial asthma, with severe allergic rhinitis, polynosis, led to disease control, changed his life and improved its quality in a short time. With the help of AST, it was possible to accurately assess the achievement of control over asthma symptoms [22]. Immunoglobulin E is an important pathogenetic link for T2 - atopic BA phenotype. Targeted therapy of children and adolescents with severe AD, targeting this biomarker, shows good results in clinical practice. Omalizumab, a humanized anti-immunoglobulin E monoclonal antibody, was approved in 2003 for the treatment of asthma. Numerous studies have shown that it improves asthma symptoms, reduces the frequency of exacerbations, and reduces unscheduled doctor visits and school absences. The presented clinical example demonstrates these findings. As a result of successful therapy, exacerbations of bronchial asthma are prevented, and the risks of future exacerbations are minimized.

Clinical studies have shown that omalizumab improves lung function [23,24]. In a teenager, we obtained a stable positive trend in spirometry data. Adolescence is a critical time to intervene in asthma management, as lung function peaks at puberty, and adolescents experience greater improvement in lung function than adults after asthma treatment [25]. This concept is clearly demonstrated in our clinical example. Biologic therapy with omalizumab was associated with improved lung function and decreased circulating eosinophils in an adolescent with severe uncontrolled asthma. The data obtained highlight the effectiveness of omalizumab in young patients and the need to optimize treatment in the early stages of the disease [26]. Omalizumab may have a significant positive impact on adolescent quality of life and disease burden [27]. Against the background of anti - IgE therapy, exacerbation of BA during respiratory infections, during physical exertion and stress was not observed. Peak flowmetry was performed regularly, and a persistent decrease in PSV variability was observed. All of these results were maintained with a decrease in ICS dosages, which made it possible to assess the low risk of asthma exacerbation. As a result of a real improvement in the control of asthma symptoms, the teenager overcame his fear associated with the frequent exacerbation of asthma, became more active in everyday life. He began to engage in physical education, sports, the quality of his life and the life of his family changed.

Currently, omalizumab is an approved and effective drug for the treatment of children with poorly controlled moderate to severe allergic asthma treated with medium and high dose inhaled corticosteroids and long-acting inhaled β2-agonists aged 6 years

and older (children and adolescents) [28]. Omalizumab is safe in children, both in clinical trials and in real clinical practice. We did not observe any unfavorable reactions during the therapy of the adolescent. The study by FU et al. [29] included 1380 children. In children with moderate to severe asthma, omalizumab reduced the frequency of asthma exacerbations (OR 0.51, 95% CI: 0.44–0.58, p < 0.001) compared with placebo, with no evidence of heterogeneity or risk of future exacerbations. The frequency of adverse events was low. Thus, in the era of personalized medicine and targeted therapy, phenotyping-based management of asthma may be an effective approach to optimize the management of patients with moderate to severe uncontrolled asthma [30-32].

Conclusion

1. Anti-IgE therapy in real clinical practice has shown its effectiveness and safety in the treatment of a teenager with severe severity, not controlled by BA. This technique is pathogenetically substantiated and effective for the treatment of T2 BA of the atopic phenotype and helps to solve the most important tasks: achieving control over asthma symptoms and preventing future exacerbations and solves problems not only of medical importance, but also social.

2. Anti-IgE therapy in specific clinical practice has shown its effectiveness not only in relation to BA, but also AR. We think that the basis of such an observation is the pathogenetic common mechanisms of various atopic diseases and their relationship.

3. The statistically significant relationship in our clinical example between a decrease in blood eosinophils and an improvement in lung function against the background of biological therapy shows the clinical significance and importance of this laboratory marker: peripheral blood eosinophilia, in the selection and evaluation of biological therapy in children with T2 BA.

Conflict of Interest

Authors declare no conflict of interest.

Source of Funding

There is no source of funding.

Informed Consent

Patient's parents provided a written voluntary informed consent for publication of this case report (signed on 28.01.2019).

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