DOI: https://doi.org/10.36691/RJA1539

Омализумаб в лечении сезонных обострений тяжёлого аллергического ринита

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АННОТАЦИЯ

Обоснование. Согласно федеральным клиническим рекомендациям, пациентам с тяжёлым персистирующим течением аллергического ринита и/или тяжёлым обострением и при неэффективности фармакотерапии 3-й линии (антигистаминные препараты, антагонисты лейкотриеновых рецепторов, назальные кортикостероиды) рекомендуется рассмотреть вопрос о назначении омализумаба, при этом нет практических рекомендаций по схемам и продолжительности терапии омализумабом при тяжёлом обострении сезонного аллергического ринита.

Цель — проведение терапии омализумабом пациентам с тяжёлым обострением аллергического ринита в сезон цветения причинно-значимых аллергенов для оценки эффективности, определения оптимального режима и продолжительности лечения.

Материалы и методы. В открытое наблюдательное несравнительное проспективное одноцентровое исследование были отобраны 10 взрослых пациентов с тяжёлым обострением сезонного аллергического ринита, вызванного пыльцой берёзы. Все они получали 3-ю линию терапии в соответствии с федеральными клиническими рекомендациями и имели неполный контроль либо его отсутствие: TNSS (общая оценка назальных симптомов) ≥2. Всем пациентам был назначен омализумаб, при этом доза и режим введения препарата подобраны в соответствии с инструкцией и учётом общего уровня IgE и веса пациента. Все пациенты ежедневно заполняли дневники выраженности симптомов и потребности в симптоматической терапии. В качестве первичной конечной точки выбрано уменьшение среднего балла комбинированной шкалы симптомов и медикаментов (Combined Medical and Symptom Score, CMSS).

Результаты. Дополнительное назначение омализумаба к ранее проводимой терапии позволило улучшить контроль над симптомами аллергического ринита у всех пациентов и уменьшить объём фармакотерапии (ΔTNSS 1,8 [95% ДИ 1,56–2,04]; p <0,001, и ΔCMSS 2,12 [95% ДИ 1,74–2,5]; p <0,001, к седьмому дню от первого введения омализумаба; ΔTNSS 2,53 [95% ДИ 2,05–3,01]; p <0,0001, и ΔCMSS 5,22 [95% ДИ 4,74–5,7]; p <0,001, к 4-й нед соответственно). Отмечено, что реализация эффекта омализумаба происходит в течение некоторого времени (от 3 до 7 дней). Поскольку в нашем исследовании продолжительность сезона не превышала 1 мес, нам удалось достичь полного контроля аллергического ринита у всех пациентов с помощью терапии омализумабом с небольшой (1–2) кратностью инъекций. Во время исследования никаких побочных эффектов не зарегистрировано.

Заключение. Назначение омализумаба пациентам с тяжёлым обострением аллергического ринита позволяет достичь полного контроля над симптомами заболевания. Учитывая механизм действия, омализумаб следует вводить по крайней мере за неделю до ожидаемого сезона пыления причинно-значимых растений пациентам с тяжёлым течением (согласно анамнестическим данным о предыдущих сезонах), которые не провели своевременно аллергенспецифическую иммунотерапию, и продолжать лечение до окончания сезона пыления причинно-значимых аллергенов.

Ключевые слова: аллергический ринит; АР; омализумаб.

Как цитировать

Павлова К.С., Куличенко Д.С., Курбачёва О.М., Дынева М.Е., Ильина Н.И. Омализумаб в лечении сезонных обострений тяжёлого аллергического ринита // *Российский аллергологический журнал*. 2022. Т. 19, № 2. С. 164–174. DOI: https://doi.org/10.36691/RJA1539

Рукопись получена: 28.04.2022 **Рукопись одобрена:** 10.05.2022 **Опубликована:** 25.05.2022

DOI: https://doi.org/10.36691/RJA1539

Omalizumab in the severe exacerbations of seasonal allergic rhinitis

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ABSTRACT

BACKGROUND: According to the Federal Clinical Guidelines, patients with severe persistent allergic rhinitis and/or severe exacerbation who failed to respond to third-line pharmacotherapy (antihistamines, leukotriene receptor antagonists, nasal corticosteroids) are advised to consider the administration of omalizumab. However, there is a lack of practical recommendations guiding the regimens and duration of the omalizumab therapy in the severe exacerbation of seasonal allergic rhinitis.

AIMS: To assess the efficacy of omalizumab additional therapy in patients with severe exacerbation of allergic rhinitis during the pollen season, and to determine the optimal regimen and duration of treatment.

MATERIALS AND METHODS: This is an open observational uncontrolled prospective single-center study. 10 adult patients with severe exacerbation of seasonal allergic rhinitis due to birch pollen were selected for the study. All of them received the third-line of therapy according to Federal Clinical Guidelines and had absence or incomplete control: Total nasal symptom score ⩾2. All of them were treated with omalizumab. The dose and regime were prescribed according to instructions that took into account the overall IgE level, as well as the patient's weight. Daily symptom diaries and the need for rescue medication levels were evaluated. The primary endpoint had a decrease in the Combined Medical and Symptom Score mean.

RESULTS: The additional omalizumab treatment improved allergic rhinitis control for all patients and also reduced the rescue medication (ΔTNSS 1.8 [95% CI 1.56–2.04]; p <0.001, and ΔCMSS 2.12 [95% CI 1.74–2.5]; p <0.001, by the end of 1 week after the first omalizumab injection; ΔTNSS 2.53 [95% CI 2.05–3.01]; p <0.0001, and ΔCMSS 5.22 [95% CI 4.74–5.7]; p <0.001, by the end of four weeks, respectively). It was noted that the omalizumab effect realization occurs for some time (3–7 days). Due to short-season pollen for birch (1–2 months), the duration of treatment in our study did not exceed one month, so we managed to achieve complete control over the symptoms in all patients by the omalizumab with a small multiplicity of injections (1–2 injections). No adverse events were registered during the study.

CONCLUSION: Omalizumab additional therapy in patients with severe exacerbation of allergic rhinitis allows control of all symptoms. Taking into account the mechanism of its action, omalizumab should be administered at least a week before the expected pollen season in patients with severe exacerbation (according to the previous seasons) who did not complete their allergen-specific immunotherapy on time, and continue therapy till the end of the pollen season.

Keywords: allergic rhinitis; AR; omalizumab.

To cite this article

Pavlova KS, Kulichenko DS, Kurbacheva OM, Dyneva ME, Ilina NI. Omalizumab in the severe exacerbations of seasonal allergic rhinitis. *Russian Journal of Allergy.* 2022;19(2):164–174. DOI: https://doi.org/10.36691/RJA1539

Received: 28.04.2022 **Accepted:** 10.05.2022 **Published:** 25.05.2022

BACKGROUND

Allergic rhinitis (AR) is one of the most common diseases in allergology and otolaryngology, characterized by IgE-mediated inflammation of the nasal mucosa (develops after exposure to an allergen) and characteristic symptoms (nasal congestion, sneezing, nasal itching and rhinorrhea), which are often accompanied by eye symptoms (lacrimation, redness, and itching) and are considered a risk factor for asthma development. Despite the fact that AR is not a life-threatening disease, it has significant impact on the patient's quality of life due to sleep disturbance, impaired work productivity, and school performance.

According to international manuals and federal clinical guidelines, basic principles of AR treatment include drug therapy, elimination measures, and allergen-specific immunotherapy (ASIT) [1, 2]. Among the pharmacological agents, nonsedative systemic antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists are distinguished, through the use of which control over the symptoms is achieved in most cases. Despite the accumulated experience of ASIT effective use and high level of evidence base on its effectiveness, in practice no more than 10% of patients receive indicated treatment due to the delayed visit to a specialist, inventory shortage of allergens, relatively high ASIT costs, and other reasons [3]. With severe exacerbation, which is most characteristic to patients with pollen sensitization, achieving control over AR symptoms using standard pharmacotherapy is not always possible. In such cases, prescribing systemic corticosteroids can be necessary, but considering the wide range of their side effects and restrictions on their use, limiting the treatment to a short term is advisable [1]. Despite the specifically indicated nonuse of systemic corticosteroids for AR treatment, doctors and even patients themselves oftentimes continue this practice during annual seasonal exacerbations.

The last decades have been devoted to the discovery and study of the biological effects of monoclonal antibodies, which have undergone a global transformation from objects of scientific research to one of the most modern and effective medicines for the treatment of patients with various pathologies. Researchers continue to study the efficacy and safety of new biologics, as well as previously known genetically engineered biologics in order to expand the range of therapeutic indications.

Considering the central role of immunoglobulin E (IgE) in the AR pathogenesis, the use of anti-IgE monoclonal antibodies in this disease seems to be the most appropriate. To date, a longstanding practice of effective omalizumab use in the treatment of severe atopic asthma and urticaria has been sustained. Data from 11 randomized clinical trials and meta-analysis on omalizumab use in AR have become the basis for expanding the indications (and updating the instructions) for its appointment and inclusion in federal clinical guidelines for AR [1, 4–6]. Thus, in patients with severe persistent AR and/or severe exacerbation, as well as with treatment failure of drugs used at the third stage of therapy (systemic antihistamines, leukotriene receptor antagonists, nasal corticosteroids), considering the administration of omalizumab is recommended in order to reduce the severity of all AR symptoms and reduce the need for symptomatic treatment drugs [1].

By reducing the level of circulating free IgE, omalizumab prevents IgE from binding to high-affinity FcεR1 and low-affinity FcεR2 receptors, preventing the release of mediators from mast cells and basophils when stimulated by a specific allergen. Anti-IgE antibodies do not bind to IgE already attached to FcεR1 and therefore are unable to initiate the activation of mast cells or basophils [7]. By reducing FcεR1 expression on dendritic cells, omalizumab can inhibit antigen (allergen) processing and its presentation to T-cells. Therefore, this may prevent their differentiation into Th2 cells, suppress the activation of Th2 lymphocytes, and lead to a decreased production of Th2 cytokines. Thus, omalizumab may act on the early and late phases of the allergic response [7, 8].

One of the first publications on the use of omalizumab in seasonal AR treatment was a double-blind, placebo-controlled study by T.B. Casale et al. (1997) [9], which included 240 patients, randomized to the appropriate treatment groups: placebo, 120 μg of omalizumab subcutaneously, 150 μg intravenously, and 500 μg intravenously 3 times 4 weeks before the expected start of ragweed blooming and during the pollen season. The effect in reducing the severity of AR symptoms was achieved in those cases where suppression of free IgE to a normal level was observed, which could be predicted by considering the initial concentration of blood serum IgE when determining the therapeutic dose of omalizumab [9].

Another double-blind, placebo-controlled study that assessed the effectiveness of omalizumab in seasonal AR was conducted by K. Okubo et al. (2006) [4]. The study included 100 children who are allergic to Japanese cedar pollen. The choice of dose and the schedule of omalizumab administration were made considering the initial IgE level and the patient's weight and were amounting to 150–375 mg every 2 or 4 weeks. The first injection was made 4 weeks before the expected start of the Japanese cedar pollen season, and then the treatment continued for 12 weeks. Decreased free IgE level correlated with decreased nasal symptoms severity, decreased nasal hyperreactivity, and decreased need for medications [4].

In a study by S. Tsabouri et al. (2014), a meta-analysis of omalizumab efficacy and safety in AR [5], 11 studies involving 2,870 patients of different ages (including children 6–11 years old, adolescents 12–17 years old, and adults) were selected. The dose and schedule of administration in most studies were selected considering total IgE baseline level and the patient's weight. Overall, a statistically significant reduction was observed in the severity of daily nasal symptoms

(–0.67 [95% CI –1.3 to –0.31], p <0.0001) and a reduction in need for symptomatic treatment (–0.22 [95% CI –0.39 to –0.05], p=0.01). No statistically significant difference was observed in the occurrence of any adverse events (relative risk 1.06 [95% CI 0.94 to 1.19]; I^2, 55%), which generally shows that omalizumab therapy has high safety profile [5].

In another meta-analysis of the efficacy and safety of omalizumab in AR, conducted by C. Yu et al. (2020) [6], 16 double-blind placebo-controlled studies published from 2000 to 2019, involving 3,458 patients (1,931 patients in the active treatment group and 1,520 in the placebo group) were selected. A statistically significant difference in favor of omalizumab was demonstrated in the following aspects: reduction in severity of daily nasal symptoms (–0.443 [95% CI –0.538 to –0.347], p <0.001), severity of eye symptoms (–0.385 [95% CI –0.5 to –0.369], p <0.001), need for symptomatic therapy (–0.421 [95% CI –0.591 to –0.251]; p <0.001), improvement in quality of life measured using Rhinoconjunctivitis-Specific Quality of Life Questionnaire (RQLQ) (–0.286 [95% CI –0.418 to –0.154], p <0.001), and overall score (odds ratio 1.435 [95% CI 1.303–1.582], p <0.001) [6].

Despite the results of placebo-controlled studies on omalizumab efficacy in AR and the possibility of its administration in AR, according to updated instructions for use and directions in federal clinical guidelines, no practical recommendations were presented on schedules and duration of omalizumab therapy for severe exacerbation of seasonal AR.

Aim of the study: This study aims to conduct omalizumab treatment in patients with severe exacerbation of AR during the pollen season of causative allergens to evaluate its effectiveness and determine the optimal schedule and duration of treatment.

MATERIALS AND METHODS

Study design

An open, observational, noncomparative, prospective, single-center study was conducted. The study was performed without a control group by comparing dependent samples (before-after analysis).

Eligibility criteria

The study included 10 patients with severe exacerbation of AR caused by the pollen season of causative allergens, with sensitization to tree pollen allergens, including birch pollen allergens. All included patients demonstrated ineffectiveness of previous combined therapy with antihistamines, antileukotriene drugs, and intranasal corticosteroids. The Total Nasal Symptom Score (TNSS) score was ⩾2. All patients were observed for a long time in the clinic of NRC "Institute of Immunology" FMBA of Russia and presented the results of previous allergological examination, which confirmed tree/birch pollen allergen sensitization.

Prior to the study, oral and written consent to participate in this observational study (subject information form and informed consent) was obtained from the patients. The criteria were previously developed considering the normative documentation OST 420511-99 Rules for conducting high-quality clinical trials in the Russian Federation, FL-61 "On Medicine Circulation" and the clinical trial protocol (Table 1).

Table 1. Inclusion/exclusion criteria

Inclusion criteria:
Patient informed written consent for participation in clinical trials
Patients of both sexes over 18 years of age
History of allergic rhinitis for at least 2 years
Confirmed sensitization to tree/birch pollen allergens
The need for symptomatic therapy with three or more drugs (stage 3 therapy, according to federal clinical guidelines)
Insufficient effect of ongoing symptomatic treatment (average TNSS score ⩾2)
Exclusion criteria:
Symptoms of respiratory viral infections at the time of participation in the study
Parasitic infection within the last 6 months
Pulmonary tuberculosis (active and inactive forms)
Oncopathology
Pregnancy, lactation
Presence of other respiratory diseases or acute conditions that can significantly affect the result of the study
Patient's unwillingness to participate in the study
Participation in other clinical trials at the time of inclusion

Terms and conditions

The study was conducted based on the NRC "Institute of Immunology" FMBA of a Russian clinic (Moscow).

Study duration

Data collection and data analysis were conducted from April 08, 2021, to July 01, 2021.

Description of medical intervention

After obtaining the signed informed consent and in case of preliminary compliance with the inclusion criteria, patients underwent physical (anthropometry, auscultation), clinical laboratory (clinical blood test, total immunoglobulin E in blood), and instrumental (spirometry) examination. All patients were consulted and examined by an otolaryngologist, which was followed by an endoscopic examination of the nasal cavity and nasopharynx.

During the first visit, clinical laboratory examination data (clinical blood test with differential leukocyte count, total IgE level to determine the dose and regimen of omalizumab treatment), TNSS, and the need for symptomatic treatment drugs, including respiratory function, have been evaluated. At this visit, patients were examined by an otorhinolaryngologist (nasal endoscopy). All patients were given diaries for daily completion. The next day after receiving the examination results, the drug (omalizumab) was administered. After the procedure, it was necessary to be under observation in the department for 2 hours.

At control visits after 1 week (visit 2), 2 weeks (visit 3), 3 weeks (visit 4), and 4 weeks (visit 5), the study physician checked the completion of daily diaries and evaluated rhinitis symptom control and the possibility of symptomatic treatment reduction.

During the fifth visit (4 weeks after treatment started), patients underwent complete physical examination similar to that performed during the first visit (results of instrumental examination, clinical blood test with differential leukocyte count, respiratory function test, otorhinolaryngological examination using nasal endoscopy were evaluated), and questionnaires' scores were analyzed.

All patients were treated with omalizumab (Xolair, Novartis Pharma Stein AG, Switzerland). The selection of omalizumab schedule and dose was performed considering the total IgE level and the patient's weight according to the instructions for use, while treatment duration depended on the duration of seasonal exacerbation.

To assess treatment safety, all adverse events that developed during the study were recorded, considering patient's subjective complaints and physical and laboratory examination data.

Primary outcome of the study

The primary endpoint was a change (reduction) in the mean combined medical and symptom score (CMSS), which is the sum of mean TNSS and the need for symptomatic treatment (medical score, MS).

Additional study outcomes

The reduced need for systemic corticosteroids; severity of conjunctival symptoms; impact on such aspects of quality of life as sleep disturbance, work productivity, and activity impairment; and physical examination results (endoscopic examination) were evaluated in this study. Visual analogue scale (VAS) was used as an additional tool to evaluate AR control [1]. Key area of focus was the timing of clinical effect onset, and as a criterion for assessing clinically significant difference, a change in mean CMSS and VAS scores by 50% from baseline was recognized.

Subgroup analysis was not performed due to the small sample size.

Outcome registration methods

All of the patients have completed the daily VAS score and diaries, which assessed severity of nasal symptoms (TNSS), the need for symptomatic treatment medications (MS), severity of conjunctival symptoms, sleep disturbance, work productivity, and activity impairment. At each evaluation visit, the doctor analyzed completed diaries and questionnaires with assessment of the possibility of changing (reducing) symptomatic treatment and collected data on adverse events.

At the beginning of the study and at control visit 4 weeks after the start of omalizumab therapy, patients underwent clinical blood test with differential leukocyte count, respiratory function test, and otorhinolaryngological examination using nasal endoscopy.

Ethical review

The study was approved by the local ethics committee of NRC "Institute of Immunology" FMBA of Russia, Protocol No. 6, dated April 7, 2021.

Statistical analysis

Due to the small percentage of extremely severe seasonal AR in the population and the high cost of omalizumab, preliminary sample calculation was not possible.

Statistical analysis of actual data was performed using statistical software package Statistica 12.0. Quantitative and ordinal values are presented as Me [q25–q75], where Me is the sample median, q25–q75 is the interquartile range (q25 is 25% quartile, q75 is 75% quartile), and Min–Max are the minimum and maximum values.

Questionnaire data (TNSS, MS, CMSS, VAS) at various control points within the same type of targeted therapy (omalizumab) were compared using Friedman test and adjusted for Dunn's multiplicity; differences were considered statistically significant at $p \leqslant 0.05$. The results are presented in the form of summary tables and graphs.

RESULTS

Objects (participants) of the study

The study involved 10 patients with severe exacerbation of seasonal AR and sensitization to tree pollen allergens, including birch pollen allergens.

When evaluating the anamnestic data, women were found to predominate in the study (6; 60%). Median age of patients was 37.4 [30.0; 45.0] years. The average duration of the disease was 5.5 [4.0; 8.0] years (from 2 to 9 years). Of associated allergic diseases, 4 (40%) patients suffered from allergic conjunctivitis; 1 (10%) patient had well-controlled atopic asthma (he received a combination of budesonide/formoterol as basic anti-asthma therapy). During spirometry, no signs of bronchial obstruction were recorded in any of the patients.

During clinical-laboratory examination, the total IgE level in blood serum of patients was found to be 326.5 [220.1; 389.9] IU/ml. All study participants received AR therapy according to the domestic and international consensus documents [1, 2]. Due to severe and uncontrolled course of AR, 6 patients received courses of systemic corticosteroids. It should be noted that patients with AR were monitored regarding compliance.

Schedule and dose of omalizumab was selected considering the total IgE level and patient's weight, and treatment duration depended on the duration of the seasonal exacerbation (Table 2).

Primary results of the study

All of the patients who completed the study reported significant reduction in severity of disease symptoms during omalizumab treatment. As a result of the study, it was shown that omalizumab was shown to suppress the intensity of rhinorrhea, nasal congestion, sneezing, nasal itching, and post-nasal drip (Table 3). As the condition improved, patients underwent a gradual decrease of symptomatic treatment, which was reflected in the MS and CMSS scales. Upon assessing the total VAS score, its value in all patients was found to be 9.0 [8.0; 10.0] before therapy and 5.0 [4.0; 6.0] 1 week after the start of omalizumab treatment.

It is worth emphasizing that improvement was already observed and recorded 1 week after the start of treatment, and this trend persisted during the next 3 weeks of observation.

According to TNSS and CMSS questionnaires, AR symptom score in patients receiving omalizumab for 4 weeks significantly decreased after 1 week (1.0 [0.9; 1.2], p=0.0002; 2.25 [2.0; 2.55], p=0.0001, respectively) compared with the data before treatment was started (figure). Regarding the need for symptomatic treatment (MS), statistically significant changes were noted only after 2 weeks of omalizumab treatment (0.15 [0.1; 0.58], p=0.0001).

At subsequent control points (after 3 and 4 weeks), an improvement in patients' condition was observed, which was reflected in the absence of symptoms in all 10 patients (see figure).

Additional study results

During endoscopic examination of the nasal cavity in AR patients, before omalizumab treatment was started, pronounced edema of the mucous membrane, causing enlargement of the nasal concha and narrowing of the nasal passages, uneven pale color of the mucosa with a cyanotic tinge, and large amount of serous or seromucosal discharge, which corresponded to an exacerbation of AR, was noted. At repeated endoscopic examination 4 weeks after the start of omalizumab treatment, all patients showed reduction in edema of the nasal concha, widening of the nasal passages, decreased amount of discharge, and normalization of color, which confirmed the restoration of nasal breathing in connection with biological therapy. The severity of these changes corresponded to a decrease in the intensity of the main AR symptoms and the changes in TNSS, MS, and CMSS.

Table 2. Dose and schedule of omalizumab administration

Patient	Dose and schedule of administration	Appearance of clinical effect from the first injection
Patient № 1	150 mg once every 4 weeks	on the 6th day
Patient № 2	450 mg once every 4 weeks	on the 3rd day
Patient № 3	600 mg once every 4 weeks	on the 5th day
Patient № 4	300 mg once every 4 weeks	on the 3rd day
Patient № 5	450 mg once every 4 weeks	on the 7th day
Patient № 6	300 mg once every 4 weeks	on the 5th day
Patient № 7	600 mg once every 2 weeks	on the 3rd day
Patient № 8	450 mg once every 4 weeks	on the 6th day
Patient № 9	300 mg once every 4 weeks	on the 5th day
Patient № 10	450 mg once every 4 weeks	on the 5th day

Note: * According to subjective patient's assessment and physical examination data.

Table 3. Change from baseline in allergic rhinitis and conjunctivitis symptom due to omalizumab treatment (*n*=10)

Symptom	Time from start of treatment				
	Before treatment	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks
Total Nasal Symptom Score (TNSS)					
Sneezing	2,8 [2,63; 2,88]	1,0 [0,6; 1,1]*	0,6 [0,2; 0,81]*	0 [0; 0]*	0 [0; 0]*
Rhinorrhea	2,51 [2,43; 2,67]	1,0 [0,9; 1,2]*	0,4 [0,0; 0,61]*	0 [0; 0]*	0 [0; 0]*
Nasal congestion	2,67 [2,55; 2,78]	1,57 [1,1; 1,88]*	0,3 [0,0; 0,4]*	0 [0; 0]*	0 [0; 0]*
Nasal itching	2,9 [2,73; 2,99]	1,2 [0,9; 1,21]*	0,1 [0,0; 0,1]*	0 [0; 0]*	0 [0; 0]*
Severity of conjunctival symptoms assessment					
Redness of the eyes	2,7 [2,59; 2,8]	0,25 [0,1; 0,5]*	0,13 [0,0; 0,18]*	0 [0; 0]*	0 [0; 0]*
Lacrimation	2,48 [2,33; 2,56]	0,14 [0,0; 0,19]*	0,1 [0,0; 0,1]*	0 [0; 0]*	0 [0; 0]*
Assessment of the impact of symptoms on quality of life					
Sleep disturbance	2,7 [2,63; 2,8]	1,1 [0,7; 1,2]*	0 [0; 0]*	0 [0; 0]*	0 [0; 0]*
Daily activity impairment	2,61 [2,55; 2,89]	1,5 [1,1; 1,7]*	0 [0; 0]*	0 [0; 0]*	0 [0; 0]*
Impaired work productivity and learning ability	2,44 [2,34; 2,53]	1,0 [0,48; 1,1]*	0 [0; 0]*	0 [0; 0]*	0 [0; 0]*
Visual analogue scale (VAS)	9,0 [8,0; 10,0]	5,0 [4,0; 6,0]*	2,0 [1,0; 2,0]*	0 [0; 0]*	0 [0; 0]*
Need for medical symptomatic therapy (MS)	2,50 [2,23; 2,67]	1,91 [1,45; 1,99]	0,15 [0,0; 0,58]*	0 [0; 0]*	0 [0; 0]*

Note: * Regarding data prior to the start of omalizumab treatment. These results are presented as Me [Min–Max].

Adverse events

During the entire follow-up period, no adverse events were registered in any of the patients, which indicated a good safety profile of omalizumab.

DISCUSSION

Summary of the primary result of the study

The results of our open observational noncomparative study showed that omalizumab administration to patients with severe exacerbation of seasonal AR and insufficient effectiveness of third-line drugs (antihistamines, leukotriene receptor antagonists, nasal corticosteroids) leads to control of all AR symptoms, decreased need for symptomatic treatment, including systemic corticosteroids, and improved quality of life.

Discussion of the primary result of the study

The results of our study are consistent with previously published data from prior randomized clinical trials, in which omalizumab efficacy in AR patients was determined by reduced nasal symptom severity, improved quality of life, and reduced use of antihistamines. Consistent data on its clinical benefit were obtained for both patients with seasonal and year-round AR. Despite the proven efficacy of omalizumab in AR, its high cost does not allow the drug to be widely used in routine clinical practice. Study protocols published previously have suggested long-term use of omalizumab for both year-round and seasonal AR (4 months or more), which increased the cost of treatment. Medical standard for managing AR patients in the Russian Federation includes prescribing omalizumab in severe cases; however, at present, this diagnostic-related group has not yet been identified, which allows prescribing omalizumab at the expense of compulsory medical insurance funds. In order to save both patient's personal funds and resources of the regional/federal fund, optimizing the protocol for prescribing omalizumab is necessary, considering the results of additional clinical trials.

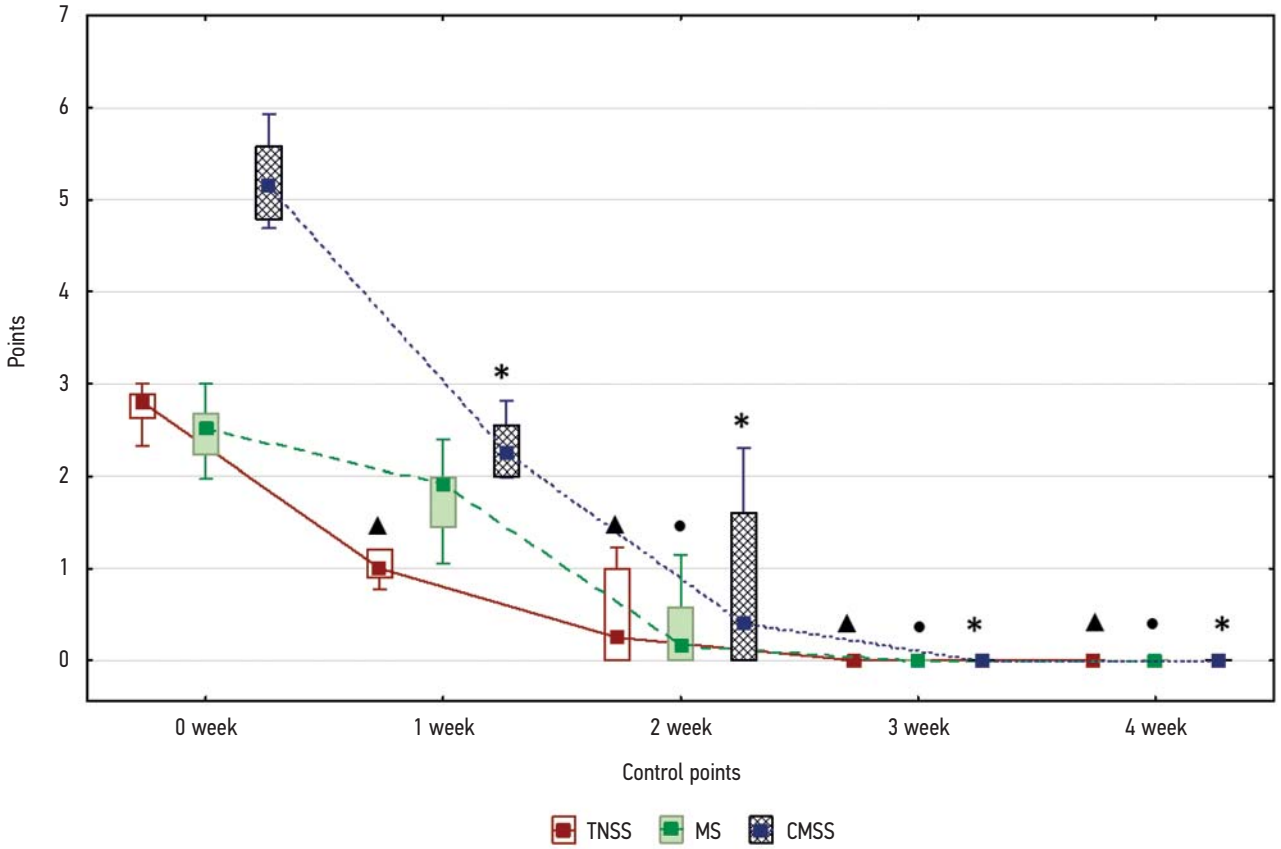

Fig. Change from baseline in Total Nasal Symptom Score (TNSS), medical score (MS), combined medical and symptom score (CMSS) due to omalizumab treatment, *n*=10.
Note: *, regarding CMSS data prior to omalizumab treatment; •, regarding MS data prior to omalizumab treatment; ▲, regarding TNSS data prior to omalizumab treatment. TNSS, Total Nasal Symptom Score; MS, medical score; CMSS, combined medical and symptom score. Data were described as Me [Q25%; Q75%] and Min–Max. Differences were considered statistically significant at $p \leqslant 0.05$.

Our study showed that this drug can be administered directly before pollen season of causative allergen plants, and duration of therapy can be calculated based on the duration of blooming season. Attempts to save money by reducing the dose of omalizumab (for example, choosing a universal dose and treatment regimen for all patients, as in urticaria) will lead to a decrease in clinical efficacy, as has been demonstrated in early studies: dose-dependent effect of omalizumab is realized when free IgE binding is maximized. By prescribing dose of omalizumab and treatment regimen individually, depending on body weight and initial (before the first administration of omalizumab) total IgE level, as in our study, meeting this condition is possible with high probability.

In our research at the start of omalizumab treatment, all patients already had signs of severe exacerbation; however, we were able to achieve control over AR symptoms in a fairly short time (3–7 days) with a persistent effect over the next 3–4 weeks. This indicates a new possibility of managing patients with seasonal AR as the alternative to the old and unsafe method of some doctors — injection of prolonged forms of systemic corticosteroids (such as Diprospan, Kenalog, etc.) during the seasonal AR exacerbation. The use of systemic corticosteroids, unlike omalizumab, is fraught with a high risk of variety of side effects. During this study, no adverse events with omalizumab have been recorded. Although the total number of administered doses of the drug in this study was limited due to the small sample size and short duration of the study, considering the results of randomized clinical trials and many years of experience of omalizumab use in routine practice, we can say that this drug has a high safety profile.

Seasonal allergic manifestations, in addition to rhinoconjunctival symptoms, are often associated with asthma exacerbation, while the course of asthma itself may be exclusively seasonal, but due to its severity, it may require the use of systemic corticosteroids. Given the efficacy of omalizumab in patients with moderate to severe asthma, based on the results of numerous randomized clinical trials, the clinical benefit of prescribing omalizumab in this situation is obvious not only in terms of AR but also asthma symptoms.

Study limitations

The main limitation of our study is the small sample size of study participants, which cannot be adequately considered representative. The small number of study participants is determined, on the one hand, by low percentage of patients with extremely severe AR and ineffectiveness of the third line

of pharmacotherapy (no more than 5% in the population) [1], on the other hand, by high cost of the drug (considering the fact that at present, the cost of AR treatment is not covered by public funding).

CONCLUSION

As a result of open observational clinical study on the use of omalizumab by patients with severe AR exacerbation due to pollen season of causative allergens, it was shown that administration of the drug was shown to help lower the severity of all AR symptoms, reduce the need for symptomatic treatment drugs, and improve quality of life. Improvement was noted already by the end of the first week from the start of therapy, and this trend continued during the next 3 weeks of observation. Implementation of omalizumab effect occurs over some time (from 3 to 7 days), so administering the drug at least a week before the expected pollen season of causative allergens to patients with expected severe exacerbation (according to the results of previous seasons, to patients that did not receive timely full-fledged ASIT courses) and continuing treatment during the entire pollen season are recommended.

In the course of our study, no adverse events were registered with omalizumab, which corresponds to scientific literature and clinical data on the use of the drug in asthma and urticaria and indicates a high safety profile of therapy.

According to scientific literature, in patients with severe AR, using omalizumab is recommended for a course of at least 3 months. Our study included patients with sensitization to tree pollen allergens, which are characterized by short period of intense blooming (1–2 months). Schedule and dose of omalizumab was selected considering the total IgE level and the patient's weight, and the duration of treatment did not exceed 1 month. Thus, with omalizumab treatment, we managed to achieve complete control over the symptoms in all 10 patients with severe AR with small injection frequency.

ADDITIONAL INFORMATION

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. K.S. Pavlova — analysis of literary sources, study concept and design writing and editing the article; D.S. Kulichenko — data collection, data processing, preparation, writing the article; O.M. Kurbacheva — study concept and design, editing an article; M.E. Dyneva — data processing, statistical analysis; N.I. Ilina — editing an article.

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