Omalizumab added to allergen immunotherapy increased the effect of therapy in patients with severe local allergic rhinitis

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ABSTRACT

Background: Allergen immunotherapy (AIT) is effective in patient with local allergic rhinitis (LAR). However, AIT may not always achieve the optimal treatment effect.

Objective: To present short study with clinical cases of LAR combined therapy with sublingual immunotherapy (SLIT) and omalizumab in patients with house dust mite (HDM) allergy and compared it to therapy with omalizumab alone.

Methods: Patients with severe LAR and hypersensitivity to HDMs were included. SLIT for HDMs was launched in a perennial protocol using SQ-HDM SLIT tablets with omalizumab. The total rhinitis symptom score (TRSS), total medication score (TMS) and combined total score (CTS) were assessed after one year.

Results: After 12 months, significant improvements in all analyzed parameters in the patients on SLIT + omalizumab therapy were observed: a reduction in the TRSS from 1.21 ± 0.33 to 0.6 ± 0.28 (p < .05), a reduction in the TMS from 2.25 ± 1.05 to 0.88 ± 0.31 (p < .05) and a reduction in the CTS from 3.46 ± 0.57 to 1.48 ± 0.51 (p < .05). This improvement in TRSS, TMS also in CTS was significantly greater than in the rest of the group with SLIT alone or omalizumab alone.

Conclusion: Omalizumab may be a valuable treatment that increases the effectiveness of immunotherapy in patients with severe LAR.

Introduction

Local allergic rhinitis (LAR) is one of the forms of local allergic diseases. The primary method of therapy is symptomatic treatment despite many studies showing the effectiveness of allergen immunotherapy (AIT) in patients with LAR who react to house dust mites (HDM), grasses, birch and tree allergens. As in other allergic diseases, AIT may not consistently achieve the optimal treatment effect in LAR patients. The present short study presents nine clinical cases of LAR combined therapy in patients with HDM allergies, in whom a satisfactory effect of AIT was not achieved. Some patients had omalizumab added to AIT. Additionally, similar patients with LAR treated with omalizumab alone were included in the study as a control group.

Material and methods

Five men and four women (mean age 32.7 ± 6.4 years) with a diagnosis of severe LAR and hypersensitivity to HDMs were included. The inclusion criteria were as follows: >18 years old; well-documented symptoms of severe persistent rhinitis according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (persistent symptoms ≥4 days/week and 4 ≥ months episode, with disturb sleep and problems at work, and with impairment of daily activity including sport, and with disturbing symptoms during day); a positive both nasal provocation tests (NPT) for extracts of allergens: D. pteronyssinus and separately for D. farinae (Allergopharma, Reinbek, Germany); negative skin prick tests (SPT) to D. pteronyssinus and D. farinae and also to grass pollen, birch, hazel, older, mugwort, cat, dog, Alternaria and Cladosporium (Allergopharma, Reinbek, Germany); negative result of allergen-specific IgE (sIgE) to inhalant allergens mentioned above in blood serum <0.15 kU/l (Thermo Fischer, Sweden); a level of total serum IgE <100 IU/L; a negative medical history of atopic diseases. Additional patients who met all the inclusion criteria were treated with omalizumab (control group). All patients during the study were allowed to use symptomatic medications. Characteristics of patients with initial symptoms, the severity of the disease and the drugs used are presented in Table 1. Patients signed a consent form to participate in the study. This study was approved by the local bioethics’ committees (KNW-1-131/N/9/K). In the patients who received symptomatic treatment with antihistamines, intranasal corticosteroids did not result in the expected improvement (reduction of symptoms according to the visual analogue scale <50% in relation to the baseline assessment) during the one year observation. For this reason, sublingual immunotherapy (SLIT) for HDMs was launched in a perennial protocol using SQ-HDM SLIT tablets (ALK-Abello, Horsholm, Denmark) containing a commercial allergen extract of 50% for D. pteronyssinus and 50% D. farinae. All patients underwent...
a one-year course of SLIT with monitoring of clinical nasal symptoms and the use of symptomatic medications. After 12 months of AIT, omalizumab (Novartis, Dublin, Ireland) therapy was added to five randomly selected patients from the entire study group and was simultaneously administered with continued SLIT. The protocol was as follows: initial doses of 150 mg every two weeks and after six weeks, 150 mg monthly during the year.

The primary outcome measurement was the mean change in the total rhinitis symptom score (TRSS), total medication score (TMS) and combined total score (CTS) during the second phase of treatment SLIT + omalizumab or SLIT continuation. Control patients received omalizumab with the initial doses of 150 mg (1 pre-filled syringe) every two weeks and after 6 weeks, 150 mg monthly during two years. They also made observed of symptoms and the use of symptomatic medications. The TRSS, TMS and CTS were assessed after one year. The TRSS is four-point symptom scale for rhinitis including an assessment of sneezing, itching, rhinorrhea, and nasal blockage. The TMS was based on summed points: 1 point for the use of oral antihistamines, 2 points for nasal corticosteroids with/without antihistamines, and 3 points for oral steroids with/without antihistamines and with/without nasal corticosteroids. The CTS is the sum of the TRSS and TMS. Daily symptoms and medication scores were monitored, after which mean monthly scores were calculated.

### Statistics

All results are presented as the mean ± SD or as a percentage. Primarily, the non-parametric tests were used because the most of data were not normally distributed. The Wilcoxon test was used to analyze differences between the groups. Only in a few cases was Student’s t-test used to evaluate the parametric values. Results for TRSS, TMS and CTS were evaluated using two-way repeated-measures ANOVA with Bonferroni’s correction. Analyses were performed using Statistica 8.12 (SoftPol, Cracow, Poland). $P < .05$ was considered statistically significant.

### Results

Characteristics of the groups are presented in Table 1. After the first year of HDM-SLIT, a significant reduction in the mean monthly TRSS was observed from 1.36 ± 0.42 (±SD) to 1.01 ± 0.29 ($p < .05$), with no significant reduction in the TMS from 2.96 ± 1.58 to 2.29 ± 1.19 ($p = .06$) and a significant reduction of the CTS from 4.32 ± 0.33 to 2.88 ± 0.56 ($p < .05$) in the studied patients. After an additional 12 months of therapy, significant improvements in all analyzed parameters in all patients were observed (Table 2). However, the TRSS, TMS, and CTS in patients with SLIT + omalizumab were significantly lower than that in participants who received an only continuation of SLIT or omalizumab alone at the end of observation (Table 2).

### Discussion

This study is the first observation of the effectiveness of omalizumab in perennial local allergic rhinitis despite different therapy combinations: with or without SLIT. Similar studies on adding omalizumab to allergen immunotherapy were conducted earlier, but for allergic rhinitis. Some authors suggest that a combined therapy with AIT promotes a better effect and a long-lasting state of tolerance to specific allergens. The first clinical trial evaluating the positive effects of a combination therapy of AIT and omalizumab on allergic rhinitis was performed in polysensitized children and adolescents in Germany. The efficacy of 24 weeks therapy with omalizumab alone in perennial allergic rhinitis was confirmed by Corren et al. This therapy significantly reduced serum-free IgE and the clinical response to nasal allergen challenges. However, omalizumab treatment for six months does not modulate synthesis of nasal IgE substantially. Extending this therapy and possibly adding

### Table 1. Characteristics of patients before initial therapy: sublingual immunotheraphy to HDM or omalizumab.

| study group SLIT | control group omalizumab |
|------------------|--------------------------|
| n = 9            | n = 6                    |
| age mean ± SD yrs | 32.7 ± 6.8               | 29.1 ± 6.1               |
| women            | 4 (44%)                  | 3 (50%)                  |
| TRSS± SD         | 1.36 ± 0.42              | 1.52 ± 0.72              |
| TMS± SD          | 2.96 ± 1.58              | 3.23 ± 1.08              |
| CTS± SD          | 4.32 ± 0.33              | 4.81 ± 0.61              |

The average duration of rhinitis yrs. therapy
| 6.2 ± 5.4        | 0.412                    |

Severity of LAR
| 0 ± 1          | 0.063                    |

Mild
| 9 ± 5         |                          |

Severe asthma
| 1 ± 1         | 0.893                    |

Legend: SLIT- sublingual immunotherapy; TRSS – mean monthly total rhinitis score; TMS – mean monthly total medication score; CTS – mean monthly combined total score; NS – nasal steroids permanently usable; AH – permanently or periodically usable; SS – systemic steroids short-time usable.

### Table 2. Changes in the studied parameters in patients and in the control group during treatment (the results before inclusion in the observation are shown in Table 1).

| subgroup continuation of SLIT n =4 | subgroup SLIT+ added omalizumab n=5 | omalizumab n=6 |
|------------------------------------|--------------------------------------|----------------|
| after the first year of SLIT       | after the next one year              | before         |
|                                   | after the first year of SLIT         | after 2 years, |
|                                   | after the next one year              | n=6            |
| TRSS± SD                           | 0.98 ± 0.31                         | 1.52 ± 0.72    |
|                                   | 0.96 ± 0.34                         | 0.87 ± 0.12    |
| TMS± SD                            | 2.52 ± 1.82                         | 3.23 ± 1.08    |
|                                   | 2.45 ± 1.21                         | 1.84 ± 0.91    |
| CTS± SD                            | 3.51 ± 0.69                         | 4.81 ± 0.61    |
|                                   | 3.42 ± 0.93                         | 2.71 ± 0.86    |

Legend: SD- standard deviation; SLIT- sublingual immunotherapy; OM- omalizumab; TRSS – mean monthly total rhinitis score; TMS – mean monthly total medication score; CTS – mean monthly combined total score;* the largest statistically significant decrease in TRSS for the SLIT + omalizumab group compared to other groups; SLIT continuation or omalizumab alone ($p < .05$);** statistically greater decrease of TMS in the SLIT + omalizumab group compared to group after SLIT continuation and to group with omalizumab alone ($p < .005$); *** statistically greater decrease of CTS in the SLIT + omalizumab group compared to group after SLIT continuation and to group with omalizumab alone ^ - significant statistically significant decrease in relation to the beginning of treatment.
SLIT has a chance to reduce IgE secretion in the nasal mucosa. This requires further research. Another study is more concerned with seasonal allergic rhinitis. Klunker et al. demonstrated the potential mechanism in vitro: IgE-facilitated CD23-dependent allergen binding to B cells was prevented by combination therapy with AIT and omalizumab compared with either treatment alone. The obtained significant clinical improvement and, above all, a substantial reduction in symptomatic treatment in the second year of SLIT treatment and after the addition of omalizumab may indicate the effectiveness of such treatment in local allergic diseases. Combined SLIT therapy with omalizumab in local allergic rhinitis is the first treatment method used. It may be an innovation in managing this type of patient in whom only a partial effect has been achieved after SLIT. However, this requires extensive research as the current observation is tiny and has significant limitations: small groups, short time of observation, and no monitoring of biomarkers of immunotherapy efficacy. Also, clinical symptoms in the control group treated only with omalizumab were slightly more intense, which may have influenced the results. Also, the shorter treatment time with omalizumab in the control group than in the other groups could affect the final effect of the study.

In conclusion, omalizumab may be a valuable treatment that increases the effectiveness of immunotherapy in patients with severe LAR.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
The author(s) reported there is no funding associated with the work featured in this article.

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References
1. Eguiñor-Gracia I, Pérez-Sánchez N, Bogas G, Campo P, Rondón C. How to diagnose and treat local allergic rhinitis: a challenge for clinicians. J Clin Med. 2019;8(7):1062. doi: 10.3390/jcm8071062.
2. Rondon C, Blanca – Lopez N, Aranda A, Herrera R, Rodriguez BJ, Canto G, Mayorga C, Torres MJ, Campo P, Blanca M, et al. Local allergic rhinitis: allergen tolerance and immunologic changes after preseasonal immunotherapy with grass pollen. J Allergy Clin Immunol. 2011;127(4):1069–1071. doi: 10.1016/j.jaci.2010.12.013.
3. Rondon C, Campo P, Salas M, Aranda A, Molina A, Gonzales M, Galindo L, Mayorga C, Torres MJ, Blanca M. Efficacy and safety of D. pteronyssinus immunotherapy in local allergic rhinitis: a double-blind placebo-controlled clinical trial. Allergy. 2016;71 (7):1057–1061. doi: 10.1111/all.12889.
4. Augé J, Vent J, Agache I, Airaksinen L, Campo Mozpo P, Chaker A, Cingi C, Durham S, Fokkens W, Gevaert P, et al. EAACI position paper on the standardization of nasal allergen challenges. Allergy. 2018;73(8):1597–1608. doi: 10.1111/all.13416.
5. Kopp MV, Hamelmann E, Bendiks M, Zielen S, Kamin W, Bergmann KC, Klein C, Wahn U. DUAL study group. Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. Pediatr Allergy Immunol. 2013;24 (5):427–433. doi: 10.1111/pai.12098.
6. Kopp MV, Hamelmann E, Zielen S, Kamin W, Bergmann KC, Sieder C, Stenglein S, Seyfried S, Wahn U. DUAL study group. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. Clin Exp Allergy. 2009;39(2):271–279. doi: 10.1111/j.1365-2222.2008.03121.x.
7. Corren J, Diaz-Sanchez D, Saxon A, Deniz Y, Reimmann J, Sinclair DS, Davancaze T, Adelman D. Effects of omalizumab, a humanized monoclonal anti-IgE antibody, on nasal reactivity to allergen and local IgE synthesis. Ann Allergy Asthma Immunol. 2004;93(3):243–248. doi: 10.1016/S1081-1206(10)61495-0.
8. Klunker S, Saggard LR, Seyfert-Margolis V, Asare AL, Casale TB, Durham SR, Francis JN; Immune Tolerance Network Group. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: inhibition of IgE-facilitated allergen binding. Allergy Clin Immunol. 2007;120(3):688–695. doi: 10.1016/j.jaci.2007.05.034.