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To cite this article: Askin Gülsen, Sönke Wallis & Uta Jappe (2019): Combination of immunotherapies for severe allergic asthma, Journal of Asthma, DOI: [10.1080/02770903.2019.1658204](https://doi.org/10.1080/02770903.2019.1658204)

To link to this article: <https://doi.org/10.1080/02770903.2019.1658204>



Published online: 05 Sep 2019.



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CASE REPORT



Combination of immunotherapies for severe allergic asthma

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ABSTRACT

Introduction: Difficult-to-treat or severe persistent asthma accounts for 5–10% of the asthma population worldwide. However, this group of patients creates a higher burden on health systems due to their morbidity and need for long-term and additional treatment. Biological drugs constitute an alternative therapy in the treatment of patients with refractory asthma. In cases where inhalant allergy is part of the pathomechanism, allergen-specific immunotherapy (SIT) is a causative treatment option for allergic asthma. However, SIT is contraindicated for uncontrolled asthma and cannot be administered according to the guidelines. This is due to the risk of further worsening of uncontrolled asthma during treatment.

Case study: We herein report a case of a 67-year-old male with severe allergic asthma who was successfully treated with SIT after asthma control was achieved by using target treatments.

Results: Complete control of asthma was achieved, and SIT with allergens from early flowering trees (birch-alder-hazel) was administered. Further, no asthmatic exacerbations or decrease in respiratory function occurred during the 15 months of treatment with mepolizumab. He did not need any oral glucocorticosteroids.

Conclusion: The case report presented here suggests the effectiveness of an individualized approach and phenotype-specific treatment of patients who cannot receive allergen-specific immunotherapy due to the contraindication uncontrolled asthma and who receive SIT after asthma control is achieved by using target treatments.

ARTICLE HISTORY

Received 15 July 2019
Revised 15 August 2019
Accepted 17 August 2019

KEYWORDS

specific immunotherapy;
uncontrolled asthma;
omalizumab; mepolizumab

Introduction

Difficult-to-treat or severe persistent asthma accounts for 5–10% of the asthma population worldwide (1). However, this group of patients creates a higher burden on health systems due to their morbidity and need for long-term and additional treatment (2). According to the latest Global Initiative for Asthma (GINA) guidelines, high dose inhalers and oral corticosteroids are required to ensure asthma control during treatment (3). Omalizumab is recommended for patients with moderate to severe uncontrolled allergic asthma with IgE levels of 30–700 kU/l in the United States of America (30–1500 kU/l in Europe), positive skin prick test, or positive results for IgE-antibodies specific for a perennial allergen (4). In addition, mepolizumab, an interleukin (IL)-5 monoclonal antibody for patients with eosinophilic asthma (baseline blood eosinophil

count above 150/ μ l or a history for blood eosinophil count above 300/ μ l) was shown to effectively treat this patient group (5).

In order to decide on the adequate treatment, severe asthma patients should be explored for potential immediate type reactions to inhalant allergen sources, like pollen or house dust mites. In cases where a clinically relevant specific allergic sensitization is detected, an allergen-specific immunotherapy (SIT) should be initiated. SIT can be applied in patients with asthma as long as the asthma is controlled, because according to treatment guidelines, uncontrolled asthma is a contraindication for SIT (6). This is due to the possibility of further worsening of uncontrolled asthma following therapeutic allergen administration. We herein present a case of a patient with severe allergic asthma in whom asthma control was achieved by biologicals to enable SIT.

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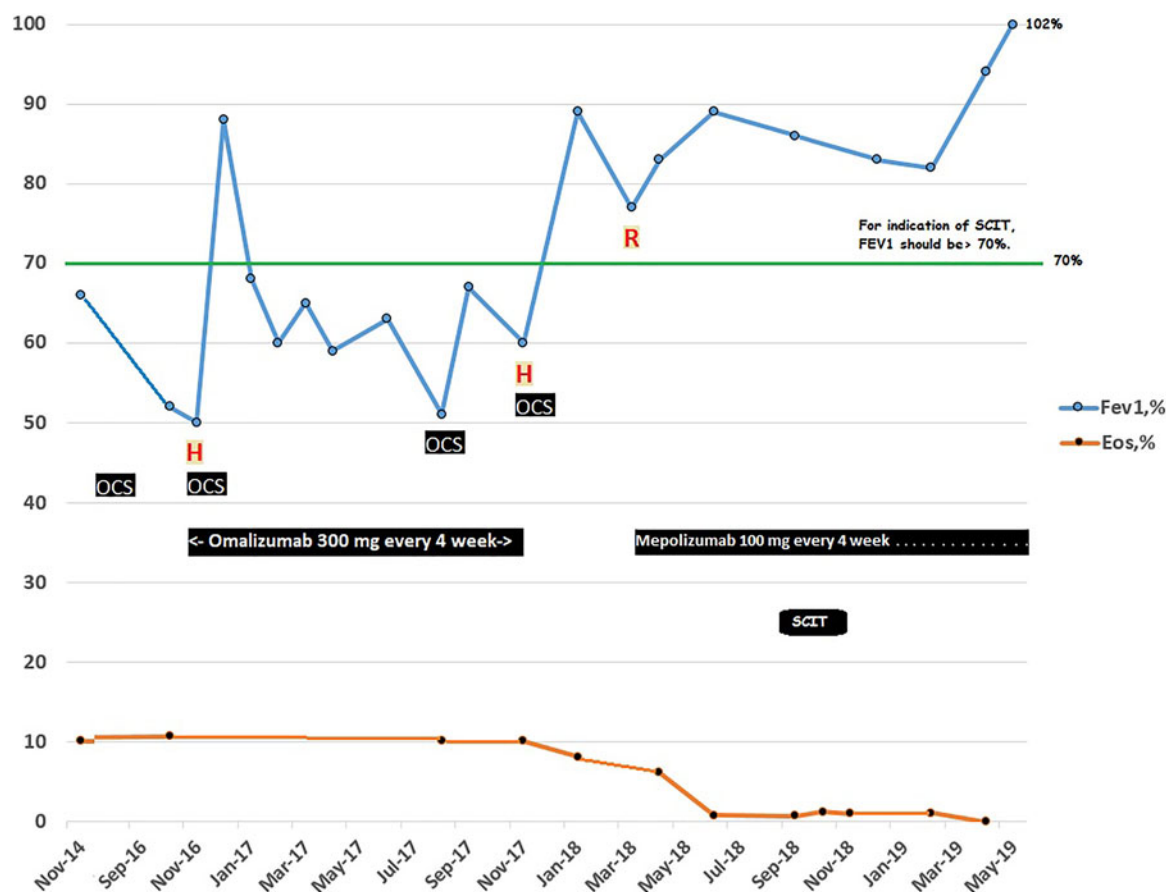


Figure 1. Synopsis of treatments and laboratory findings. Note: (H, hospitalization; OCS, oral corticosteroid; R, rehabilitation; SCIT, subcutan immunotherapy; FEV1, forced expiratory volume in 1 second).

Case study

A 67-year-old male nonsmoker with a history of severe allergic asthma and polyposis nasi since 1984, additionally developed allergic rhinoconjunctivitis with symptoms mainly in late March and early April and pollen-associated food allergy in ca. 2008. For many years he suffered from nasal congestion and anosmia. However, when spending two to three weeks of holidays in the Swiss alpes, his sense of smell returned and exercise capacity increased significantly. After having returned to Northern Germany, the symptoms regularly relapsed. The patient had been taking budesonide plus formoterol, nasal and oral corticosteroids for many years to control his symptoms, but his condition had worsened continuously since 2014. Samter-Trias was not considered because the patient had previously tolerated 100 mg acetylsalicylic acid. Respiratory function tests performed in 2014 revealed a forced expiratory volume in one second (FEV₁): 2.03 L –66%; and FEV1/forced vital capacity (FVC): 57%. The total IgE concentration was 164 kU/l and blood eosinophil count 840/μl (10.1%). Between

2014 and 2016, he was admitted to the hospital many times, and high-dose inhaled and short-term oral glucocorticosteroids were frequently used. At the time of referral to our polyclinic, the FEV₁ was 1.55 L (52%). We decided to initiate omalizumab treatment. From November 2016 onwards, omalizumab was administered subcutaneously at a dosage of 300 mg every 4 weeks for a period of 12 months. At the end of the treatment, the FEV1 was 1.78 L (60%), the total IgE concentration 601 kU/l, and blood eosinophil count 840/μl (10.0%). The allergic bronchial asthma was not satisfactorily controlled despite the extended drug therapy. At least three episodes of asthma exacerbations requiring hospitalization occurred during omalizumab treatment.

In expanded allergic examinations, specific IgE antibodies against house dust mites and fungi (such as *Alternaria*, *Aspergillus* and *Penicillium*) could not be detected. However, specific IgE antibodies against the following inhalant allergens: birch (Bet v 1) 14.30 kU/l - RAST class 3, timothy grass (rPhl p 1 + rPhl p 5 b) 2.02 kU/l - RAST class 3, alder 7.48 kU/l - RAST class

3, and hazel 6.20 kU/l- RAST class 3 were found. Nevertheless, SIT could not be administered owing to the pulmonary symptoms and impairment of lung function. Considering the patient's eosinophilia and high IgE values, it was decided to discontinue the omalizumab and initiate mepolizumab treatment. Mepolizumab 100 mg was administered subcutaneously every 4 weeks, beginning in April 2018. During the treatment, the FEV₁ was 2.53–2.98 L (86–102%) (Figure 1). Blood eosinophilia decreased to 70/ μ l (0.8%) following the first dose and remained at 70–100/ μ l (0.7–1.2%).

Results

Complete control of asthma was achieved, and SIT with allergens from early flowering trees (birch-alder-hazel) was administered weekly via subcutaneous injection for 4 weeks in October 2018 to be continued in autumn 2019 and 2020. In the following time period, significant improvement was observed in the patient's symptoms and quality of life. In the spring of 2019, the patient's symptoms of rhinoconjunctivitis and the need for nasal corticosteroids regressed. He did not need any oral glucocorticosteroids. Further, no asthmatic exacerbations or decrease in respiratory function occurred during the 15 months of treatment with mepolizumab.

Discussion

New biological drugs have improved the treatment of difficult-to-treat or severe asthma, while bronchial thermoplasty has also provided an alternative treatment for some severe cases (3,7). The allergen-specific immunotherapy, which is the only causative anti-allergic treatment apart from allergen avoidance, induces a decrease in the daily medication requirement and improvement in symptom scores in people with IgE-mediated allergic diseases (3). However, timing and choosing the appropriate treatment option is challenging since reliable biomarkers for treatment efficacy have not yet been established. For moderate and severe allergic asthma, omalizumab is the gold standard treatment and has long been recommended in the GINA guidelines (3). However, as in our case, these treatments are not effective in some patients. Further, IL-5 is the most important cytokine produced by type-2 T helper cells and mast cells. It is responsible for the proliferation, maturation, activation, and survival of eosinophils (8). Therefore, IL-5 represents a specific target for the treatment of eosinophilic

diseases, and presents an alternative treatment option for patients with difficult-to-treat asthma that is refractory to standard treatments. Our patient did not experience symptom improvement during the one year of omalizumab treatment. Therefore, and because of the high blood eosinophil count, the treatment was switched to mepolizumab. Eventually, asthma control was achieved, so that the contraindication for SIT no longer existed, and it was initiated in parallel to mepolizumab. In addition to our positive results, the replacement of omalizumab with mepolizumab is still under investigation (9). However, a recent case report showed that a combination of both, omalizumab and mepolizumab, may be useful for patients with high total serum IgE and eosinophilia (10).

Conclusion

The case report presented here suggests the effectiveness of an individualized approach and phenotype-specific treatment in patients who cannot receive allergen SIT due to uncontrolled asthma. Mepolizumab may be a good choice if adequate clinical response and control has not been achieved with omalizumab.

Declaration of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Funding

This work was supported by the Federal Ministry for Science and Education (BMBF), German Center for Lung Research.

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