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Combination therapy of specific aeroallergens immunotherapy and omalizumab, in children with severe asthma

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Abstract
Background: In most cases, severe asthma in children has an allergic etiology, but allergen-specific immunotherapy (AIT) is contraindicated.
Objective: This study aimed at analyzing the safety and efficacy of AIT in patients with severe asthma treated with omalizumab (OM).
Methods: A descriptive real-life study was carried out by reviewing medical records. Effectiveness was measured by the degree of control (CAN questionnaire), number of hospitalizations per year, number of exacerbations per year, and maintenance treatment and lung function (FEV1). Some adverse reactions occurred (AAI-EAACI-WAO guidelines).
Results: The retrospective study included 29 patients up to 18 years of age with severe asthma with OM plus AIT treatment. AIT treatment was started in a cluster schedule when patients treated with OM achieved disease control. Before starting AIT, patients were treated with OM for 1 year for achieving asthmatic control. AIT to mites (51%), *Alternaria* (37.9%), or pollens (10.3%) was administered. After one year with OM plus AIT,statistically significant differences in CAN scores and FEV1 measures were observed ($P < 0.001$). No patients under treatment with OM plus AIT required hospital admission. During the clustering schedule, only 3/64 doses showed systemic adverse reactions. During the AIT maintenance treatment, 348 doses were administered, with no significant adverse reactions.
Conclusion: In this population-based study in children with severe asthma, the combined treatment with OM plus AIT was safe and effective. This strategy allows these pediatric patients to be safely treated with AIT.

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Introduction

A high degree of morbidity and mortality is associated with severe asthma in children. It is characterized by controlled symptoms with high doses of inhaled or oral corticosteroids or by uncontrolled asthma symptoms despite such therapy. In addition, this condition exerts a substantial burden on patients' care,[1-3] their families, and the health service. Unscheduled medical visits and even the use of emergency rooms and hospital admissions are often required.

In most cases, severe asthma in children has an allergic etiology. Specific allergen immunotherapy (AIT) is the only immunomodulatory treatment available to treat allergic disease.[4,5] But AIT is ineffective in severe uncontrolled asthma.

Omalizumab (OM) is a biological treatment approved for moderate-to-severe persistent allergic asthma management[7] in patients of at least 6 years of age. Some authors have obtained successful results from the combined therapy with specific (AIT) and OM for allergic rhinitis, asthma, allergy to hymenoptera venom, and food allergy.

However, there is currently little clinical experience with combined treatment with AIT and OM in severe pediatric asthma. After controlling asthma with OM, AIT can be safely and effectively administered.[8-10] This study aimed to analyze the safety and effectiveness of AIT in pediatric patients with severe asthma receiving OM treatment.

Methods

This was a retrospective, descriptive, real-life, postauthorization study with a different design than the prospective follow-up (EPA-OD) according to the evaluation of the Spanish Drug Agency (AEM, for its initials in Spanish). This study has been approved by the ethics committee of our hospital and carried out by reviewing the medical records.

All clinical records of patients up to 18 years of age, with a diagnosis of severe allergic asthma and GINA stage 5 receiving combined treatment with aeroAITand OM from 2015 to 2019 were included. Inclusion/exclusion criteria are shown in Table 1.

We guarantee that all the information in the study will be treated as stipulated by regulation 2016/679 of the European Parliament and of the Council of April 27, 2016, on data protection (GDPR), and Organic Law 3/2018 of December 5, on the protection of personal data and guarantee of digital rights. Data were obtained retrospectively from patients' medical histories.

Table 1 Inclusion and exclusion criteria.

Inclusion criteria
Patients up to 18 years of age under follow-up at our hospital.
Diagnosed with severe allergic asthma and under treatment with omalizumab.
Sensitization to mites, *Alternaria* or pollen (prick test with >3 mm or specific immunoglobulin E of >0.35 KU/L).
Under treatment with immunotherapy associated with omalizumab for at least 1 year.
Exclusion criteria
Loss of follow-up or inability to collect data from patients' medical history.

The primary endpoint to evaluate safety was the number of local and systemic adverse reactions to immunotherapy classified according to the 2010 AAI-EAACI-WAO guidelines.[11,12]

Effectiveness was measured by the degree of control (CAN questionnaire), number of hospitalizations per year, number of exacerbations per year, maintenance treatment needed, and lung function (FEV1).

Data on type of immunotherapy extract, allergens included, doses administered, age at treatment start, duration of OM treatment, AIT, sex, and other concomitant allergic diseases were collected.

CAN questionnaire scores were collected before starting treatment with OM and combined treatment with OM plus AIT and 1- and 2 years after combined treatment with OM plus AIT. Two determinations : one before treatment initiation with OM and the other one- and two years after the combined treatment initiation, were made to evaluate the number of hospitalizations per year and of exacerbations per year.

Maintenance treatment needed (according to GEMA guidelines' therapeutic steps) and lung function (FEV1) were collected before starting OM and AIT and 1 year after combined treatment to evaluate effectiveness.

The administration of OM and the indication of AIT are regular practices in the treatment of asthma; for this reason, we request the ethics committee to make an exception to the requirement to obtain informed consent, according to the classification of our study by the Spanish drug agency.

Statistical study

Quantitative variables have been described using the mean and standard deviation for normal distribution and the median and 25th and 75th percentiles for nonnormal distribution. Qualitative variables were described using frequencies and percentages.

Inference on effectiveness was studied using repeated-measures analysis of variance (ANOVA) of CAN questionnaire scores. FEV1 values and maintenance treatment needed was used to describe the reduction in the number of exacerbations and hospitalizations before treatment with OM and after 1 year with combined therapy with OM and ATI. The data were compared using Wilcoxon nonparametric test for paired data. For all analyses, P values <0.05 were considered statistically significant. Statistical analyses were performed with the IBM SPSS software Version 25 (IBM SPSS Statistics, Armonk, NY).

Results

The study included 29 patients, 21 (72.4%) of whom were boys up to 18 years of age with severe asthma and treated

with OM and AIT. Before starting AIT, they were treated with OM for 1 year to achieve asthma control.

Once their disease was controlled and remained that way after decreasing the maintenance treatment, AIT specific to mites or *Alternaria* in a cluster schedule was administered, depending on the sensitization they showed. AIT was administered subcutaneously at the daycare hospital, which was equipped for the treatment of allergic reactions and close to the emergency and intensive care units.

Patients' age at the start of treatment with OM and combined treatment with AIT and OM and duration of both therapies at the time of analysis are shown in Table 2.

The median immunoglobulin E value before treatment with OM was 719 IU/mL (p25 of 345 IU/mL and p75 of 1448 IU/mL).

Fifteen (51.7%) patients received treatment with a mixed extract of *Dermatophagoides pteronysinus* and *D. farinae*, 11 (37.9%) were treated with an *Alternaria* extract, and three (10.3%) with a pollen extract.

All our patients had comorbidities associated with their severe asthma: 10 (34.4%) had atopic dermatitis, 11 (37.9%) had a food allergy, and 19 (65.5%) had allergic rhinitis.

The following variables were collected: CAN questionnaire scores, lung function (FEV1), maintenance treatment needed, number of exacerbations, and number of hospital admissions to evaluate the effectiveness of the treatment.

We observed a decrease in the CAN questionnaire scores (Figure 1) and maintenance treatment (Figure 3) and an increase in FEV1 values (Figure 2) throughout the entire treatment, indicating efficacy in asthma control. When comparing these values using the repeated-measures ANOVA test, statistically significant differences were found, showing a decrease in the CAN questionnaire scores ($P < 0.001$) and in the therapeutic maintenance step ($P < 0.001$), and an increase in FEV1 ($P < 0.001$) throughout the study period.

Comparisons (Table 3) between the CAN questionnaire scores before starting OM and 2 years after combined treatment, before starting AIT and 2 years after combined treatment, and after 1 year with OM plus AIT and at 2 years of treatment showed statistically significant differences ($P < 0.001$). All 29 patients required systemic corticosteroids before OM treatment, and none required any corticosteroids 1 year after the combined treatment. Comparisons (Table 4) between FEV1 measurements at the start of OM treatment, before the start of AIT, and 1 year after combined treatment (OM plus AIT) showed statistically significant differences ($P < 0.001$)

The number of hospital admissions per year because of asthma decreased significantly. No patients receiving treatment with OM plus AIT for 2 years required hospital admission. When comparing these values using the Wilcoxon test for paired measures, statistically significant differences were found ($P < 0.001$).

Immunotherapy was administered in a cluster schedule. About 26 patients received treatment with polymerized extracts, and three were treated with depot extracts.

During this schedule, 64 doses of immunotherapy were administered, (52 (81.2%) polymerized extracts and 12 (18.8%) native extracts). Adverse reactions were seen in 10 administered doses and seven local reactions. Only three grade 3 (4.6%) systemic reactions were reported(one urticaria and two bronchospasms). None of them required hospital admission and it the AIT was not discontinued.

During the AIT maintenance treatment, 348 doses were administered, and no significant adverse reactions were observed.

Discussion

This was a retrospective, real-life, observational study to review medical records in 29 children with severe asthma who received combined treatment with OM and AIT in our hospital. We observed statistically significant differences in the CAN questionnaire scores and FEV1 measures after 1 year with OM plus AIT ($P < 0.001$). No patients treated with OM plus AIT required hospital admission. During the clustering schedule, only 3/64 doses showed systemic adverse reactions. During the AIT maintenance treatment, 348 doses were administered, and no significant adverse reactions were observed.

Most cases of severe asthma in the pediatric population are atopic asthma and sensitization to aeroallergens. However, AIT is currently inadvisable[4,5] in patients with poorly controlled severe asthma because of the high risk

Table 2 Age at start of treatment and duration of treatments (years).

N=29	Mean (min; max), years	Standard deviation
Age at start of OM	9 (4;16)	3.6
Age at start of AIT	10 (5;17)	4
Duration of OM treatment before starting AIT	1 (1;3)	0.9
Duration of combined treatment (OM+ ITA)	2.5 (1;5)	1.1
Duration of OM treatment	3.7 (1;8)	1.6

OM, omalizumab; AIT, allergen immunotherapy; Min, minimum; Max, maximum.

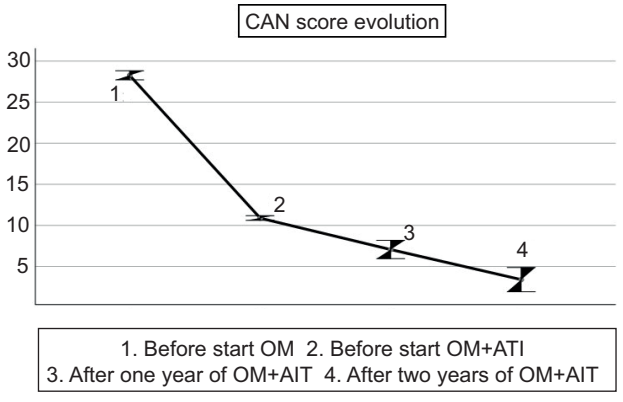

Figure 1 CAN questionnaire scores throughout the treatment.

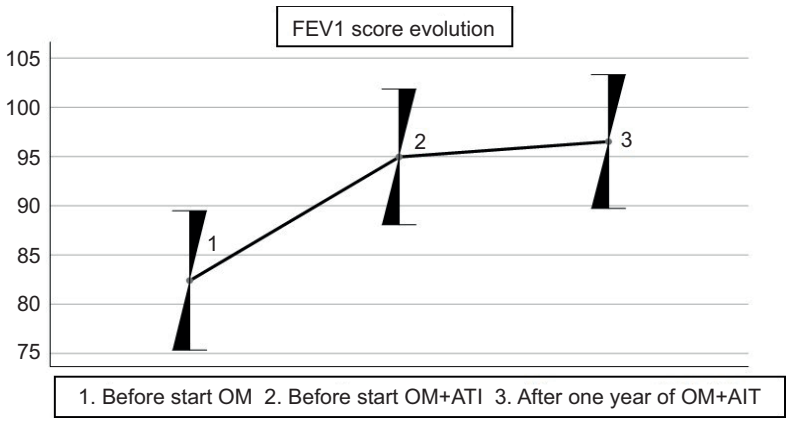

Figure 2 FEV_1 values throughout the treatment.

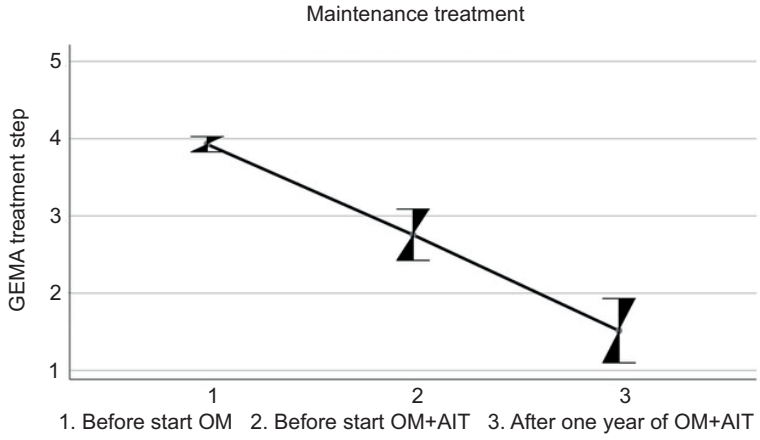

Figure 3 Maintenance treatment.

Table 3 Efficiency variables: CAN questionnaire (asthma control in children) score of <9.

CAN questionnaire	Mean	p25-p75	P value*
1. Before start of OM	28.2	27-29.5	
2. Before start of AIT	10.9	9-11.5	
3. After one year of OM+AIT	7.07	7-9	<0.001
4. After two years of OM+AIT	4	0-8	<0.001

*t-student.
OM, omalizumab; AIT, allergen immunotherapy.

Table 4 Efficiency variables: FEV1 (L/s).

Lung function - FEV_1(%)	Mean FEV_1(%)	FEV_1(%) (p25-p75)	P* value
Before start of OM	78	(65.5-97.5)	
Before start of AIT	92	(81.5-105.8)	
After one year of OM+AIT	96	(85-103)	<0.001

*t-student.

for adverse effects. Previous studies have shown that AIT has better results in patients with severe allergic rhinitis, and the same can be expected with severe asthma.[13,14] The evidence on the efficacy of AIT in severe asthma in children is quite limited because of the difficulties in conducting clinical trials in children and the contraindication of AIT for severe asthma.

There are few studies on severe asthma and immunotherapy in the pediatric population. In a study conducted by Tsai et al.[15] , 40 children aged 5 to 14 years with moderate-to-severe asthma were randomly assigned to receive a mite extract subcutaneously. After 6 months of follow-up, no systemic reactions were recorded, and patients treated with immunotherapy improved their symptoms than those who did not receive this treatment (P < 0.01). This study only included patients with severe asthma that received treatment with OM (Table 5). But also observed the safety and improvement in those patients with severe asthma who underwent AIT plus OM therapy.

Only very few studies on the efficacy of combined therapy with OM and AIT in the treatment of severe asthma in children exist, with only some showing the safety and efficacy of OM before the treatment or in combined treatment in adult patients with severe allergic asthma, with the achievement of disease control and a decrease in the severity of the symptoms.[16-18] We have observed similar

Table 5 Efficacy variables: exacerbations/year.

Clinical improvement	Exacerbations/ year	Value (p25–p75)	p value*
Before start of OM	6	5–7	
Before start of OM+ATI	1	0–2	<0.001
After one year of OM+AIT	None		

*Wilcoxon test.
OM, omalizumab; AIT, allergen immunotherapy

results in our pediatric patients. In our experience, when patient stops OM, they are still symptom-free with immunotherapy. Unfortunately, our study did not aim to compare the duration of OM treatment with or without ATI. We stopped immunotherapy when the 4 years of treatment ended, and our patients remained under control with low doses of inhaled therapy. We believe that the efficacy of immunotherapy should be similar to patients with nonsevere asthma, but a longer follow-up is necessary to assess their long-term efficacy.

Massanari et al.[19] published a multicenter, double-blind, randomized study in adult patients with symptomatic asthma to evaluate the effect of OM on the tolerability of AIT for 1–3 extracts and showed that the use of OM in patients with severe asthma was associated with fewer systemic allergic reactions to specific immunotherapy and facilitated reaching the maintenance dose of immunotherapy as observed in our pediatric patients, where all 29 reached the target immunotherapy doses without serious adverse events and improved asthma control.

Our safety results are consistent with those observed by Har and Jung Lee,[20] published a retrospective safety study that only included the pediatric population and compared AIT, OM, and combined AIT plus OM treatments. Results indicated that the combined therapy with OM and AIT in children is safe and allows the administration of AIT. Only 2/29 patients had a systemic reaction during the clustering schedule (2/64 doses administered), which resolved with oral or inhaled treatment. After 412 AIT doses were administrated, none of our severe asthma patients treated with OM required adrenaline or hospitalization.

The results of our study were limited by the number of patients included and the retrospective design. But our results showed statistically significant differences in efficacy, and studies such as those conducted by Har et al.[20] support the safety of the combined treatment. In our opinion, offering an immunotherapy option to our patients with severe allergic asthma is the correct option since it is the best treatment option for asthma controlled with OM.

Conclusion

In our population-based study in children with severe asthma, the combined treatment of omalizumab and AIT was safe and effective. This strategy gives pediatric patients with severe asthma an opportunity to be safely treated with AIT. Inducing a change in their immune response would change the severity phenotype, improve patients' quality of life, and prevent airway remodeling. Just as the studies carried out with adult patients, they can even raise the need to develop standardized protocols for this combined treatment to optimize the management of severe allergic asthma.

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