Conflict of interest

AGDA has received lecture and meeting fees from Novartis. ALN has received lecture fees from Novartis. ANG has received consultancy/advisory board fees and grants from Novartis and GSK, and lecture fees from Novartis. AMR has received lecture fees and grants from Novartis. APM has received lecture and advisory board fees from Novartis and GSK. CRJ has received speaker and advisory board fees from Novartis and GSK. EV has received meeting fees from Novartis. JLB has received lecture and advisory board fees from Novartis and GSK. JTB has received advisory board and conference fees from Novartis. LMG has received scientific advice and conference fees from Novartis. LVN has received lecture fees from Novartis. MACR has received lecture fees from Novartis. MBG has received lecture fees from Novartis. MSM has received meeting fees from Novartis. MTG has received lecture fees from Novartis. RRG has received advisory board fees from Novartis. TGB has received lecture fees from Novartis. VSS has received lecture fees from Teva and Novartis. AAM, AF, AVS, CAF, EBA, ECA, GRC, JBG, JNM, LMP, MMFG, MG, MNC and MPA declare no conflicts of interest.

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Financial support

The study received an unrestricted grant from Novartis. Novartis did not have any role in the design of the study, in the collection, analysis or interpretation of data, or in the elaboration of the manuscript. Therefore, the views expressed here are only based on the author's opinions.

Abstract

Background: Various studies have assessed omalizumab outcomes in the clinical practice setting but follow-up and/or number of patients included were limited. We aim to describe the long-term outcomes of pediatric patients with severe persistent allergic asthma receiving omalizumab in the largest real-life cohort reported to date.

Methods: ANCHORS was a multicenter, observational, retrospective cohort study conducted in 25 Pediatric Allergy and Pulmonology units in Spain. We collected data of patients <18 years and initiating omalizumab between 2006-2018, from the year prior to omalizumab initiation to discontinuation or last available follow-up. The primary outcome was the evolution of the annual number of moderate-to-severe exacerbations compared to the baseline period.

Results: Of the 484 patients included, 101 (20.9%) reached six years of treatment. The mean±standard deviation number of exacerbations decreased during the first year of treatment (7.9±6.6 to 1.1±2.0, $p<0.001$) and remained likewise for up to six years. The other clinical parameters assessed also improved significantly during the first year and stabilized or continued to improve thereafter. The percentage of patients experiencing adverse events was consistently low, and the main reason for discontinuation was good disease evolution.

Conclusion: In this large, long-term, observational study, moderate-to-severe exacerbations decreased significantly from the first year of treatment with omalizumab. The beneficial effect was maintained in the long-term, along with a good safety profile. Our results position omalizumab as an effective long-term treatment in pediatric patients with severe persistent allergic asthma.

Keywords

Children, adolescents, severe asthma, omalizumab, anti-asthmatic agents, humanized monoclonal antibodies, observational study, real-life

Key message

Clinical trials have shown the benefits of omalizumab in pediatric patients with severe allergic asthma, but the follow-ups and/or number of patients included have been limited. Real-life studies are needed in order to check the results obtained in randomized clinical trials.

To our knowledge, this is the first observational study reporting outcomes for up to 6 years of omalizumab in a large cohort of pediatric patients with severe persistent allergic asthma. Our results come to support the long-term efficacy and safety of omalizumab in pediatric patients with severe persistent allergic asthma who are unable to achieve disease control with conventional treatments. No tachyphylaxis seems to develop in the long term.

Introduction

Pediatric patients aged ≥6 years with severe persistent allergic asthma (SPAA) and unable to achieve disease control on Global Initiative for Asthma step 4 have the option to receive tiotropium bromide or targeted therapy with mepolizumab or omalizumab.[1] In line with the growing agreement on the need for pragmatic real-life data,[2] various prospective[3–7] and retrospective[8–12] studies have assessed omalizumab outcomes in real-life pediatric cohorts, but their follow-up, number of patients included or both have been limited. To determine the safety and effectiveness of omalizumab in real life, long-term follow up data from larger cohorts are needed. The study described herein follows this approach. The main objective was to describe the clinical evolution after initiating omalizumab. Other objectives included describing the patients' profile, and the effectiveness, safety, and rate and reasons for discontinuation of omalizumab.

Methods

ANCHORS (Asthma iN CHildren: Omalizumab in Real-life in Spain) was a multicenter, observational, database, retrospective cohort study conducted in 25 Pediatric Allergy and Pulmonology units in Spain. All procedures were in accordance with the Declaration of Helsinki. A central ethics committee (Hospital Universitari i Politècnic La Fe, Valencia-Spain) approved the protocol, and granted a waiver for informed consent.

During the data collection period (August-October 2018), the participating units identified all patients treated with omalizumab between 2006 and 2018. We included those who initiated at <18 years of age to treat physician diagnosed SPAA. Data were collected from the year prior to omalizumab initiation (baseline period) until omalizumab discontinuation or the last available follow-up.

The primary outcome was the evolution of the annual number of moderate-to-severe exacerbations (MSE) compared to baseline. MSE were those requiring systemic corticosteroids, emergency visits, and/or hospitalizations. As secondary outcomes, we described the characteristics of patients and analyzed the annual evolution of several clinical parameters from baseline: number of non-serious exacerbations (requiring short-acting beta-agonists only); forced expiratory volume at first second (FEV_1, % predicted); fractional exhaled nitric oxide (FeNO); maximum mid-expiratory flow (MMEF, % predicted); absolute eosinophil count; number of healthcare encounters (unscheduled visits to primary care pediatricians and specialists, asthma-related emergency visits and hospitalizations, and pediatric intensive care unit [PICU] admissions); courses of systemic corticosteroids; concomitant chronic medications for asthma; and asthma control. Asthma control was assessed through validated tools (Asthma Control Questionnaire [ACQ], Asthma Control Test [ACT], and/or the Spanish Asthma Control in Children [CAN]).[13–16] Finally, as secondary safety outcome, we described adverse events (AEs) and, as exploratory outcomes, the rate and reasons for omalizumab discontinuation.

Statistical analyses

Sample size considerations are described in the Appendix. Data extracted at each unit were pooled in a single anonymized database to conduct the statistical analyses (SAS software version 9.4). We present data and performed analyses for baseline demographic and clinical characteristics, MSE and other clinical parameters based on the effectiveness population (patients with data for the primary outcome at baseline and at least one year after omalizumab initiation). For safety outcomes, and rate and reasons for discontinuation, we used the safety population (patients who received ≥1 dose of omalizumab). In addition, we conducted a subgroup analysis by age at omalizumab

initiation (≤6 years, >6-12 years, >12 years). Also, we describe data for patients >6 years separately to assess whether the inclusion of younger patients, in whom omalizumab is not approved, may distort the results.

We analyzed questionnaire scores (QS) as a continuous and categorical variable, by classifying patients as "controlled" and "uncontrolled" according to published thresholds.[15–18] As the tool most used in Spain (CAN) as well as ACT only distinguish between "controlled" and "uncontrolled", patients classified as "partially controlled" by ACQ were considered "uncontrolled" to harmonize the three tools. For patients with more than one score on a given year, we used the worst value.

We summarized and analyzed available data without imputing missing values. For annual comparisons versus baseline, we used the t-test or Wilcoxon's test for continuous variables, and McNemar's for categorical ones. For intergroup comparisons, we used the ANCOVA or Kruskal-Wallis tests for continuous variables, and the Chi-square or Fisher's test for categorical ones. In intergroup pairwise comparisons, we applied the Bonferroni correction to account for multiplicity. All tests were two-sided, with a significance threshold of $p<0.05$.

Results

Of the 484 patients included, all formed the safety population, while 426 formed the effectiveness population (eFigure 1). Of the 484 patients, 101 (20.9%) reached six years of treatment. As only 20 (4.1%) patients continued treatment beyond this point, we present results for the first six years of follow-up, except for AEs and discontinuations. Clinical and demographic characteristics of the effectiveness population at omalizumab initiation (Table 1) did not differ substantially from those of the safety population. Characteristics for age subgroups are shown in eTable 1.

Omalizumab dosage

The mean±standard deviation (SD) monthly dose of omalizumab decreased progressively from 524.5±337.1 mg during baseline to 369.7±276.6 mg during Year 6. Similarly, the mean dosing interval shifted gradually from 3.2±1.1 to 4.0±1.6 weeks.

Efficacy outcomes

The mean±SD annual number of MSE decreased significantly from 7.9±6.6 during baseline to 1.1±2.0 during the first year of treatment with omalizumab (86% reduction). The number continued consistently low up to Year 6 (Figure 1A). Something similar happened across age subgroups (Figure 1B). ANCOVA models showed significant intergroup differences in Years 1, 2 and 4. Subsequent pairwise comparisons did not reveal significant differences except for a higher reduction from baseline in patients >12 versus >6-12 years during Year 4 (eTable 2).

During the first year of treatment, there was a significant reduction in the number of mild exacerbations (-71%), which remained consistently low up to Year 6 (eFigure 2). FeNO decreased and FEV_1 and MMEF increased significantly during the first year, remaining stable thereafter (Figure 2; see also eTable 3 for age subgroups). Absolute eosinophil count decreased 19% from baseline in the first year and continued to drop, up to 62% in Year 6 (Figure 3).

We describe disease control and evolution of QS for each tool in eFigure 3. At baseline, 28/334 (8.4%) patients were controlled as per QS. This percentage improved significantly during the first year of treatment (148/329 [45.0%], $p<0.001$) and kept increasing up to Year 6 (75/84 [89.3%]).

After 1 year of omalizumab treatment, the number of all healthcare encounters decreased significantly, with no PICU admissions from Year 2 onwards (Figure 4).

Mean±SD courses of rescue systemic corticosteroids decreased by 88% from baseline to Year 1 (4.1±3.4 vs.0.5±1.1, p<0.001) and remained low thereafter (0.2±0.7 during Year 6).

The number of concomitant chronic medications was significantly reduced in Year 1 and remained lower than baseline up to Year 6. There was an apparent increase in the proportion of patients receiving ≥2 medications by the end of follow-up (Figure 5A). The proportion of patients receiving each type of medication followed a similar pattern, with an apparent increase from Year 5 in the use of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) (Figure 5B). There was a significant drop in the mean±SD daily dose of ICS from baseline to Year 1 (867.3±474.5 vs. 663.4±431.4 µg budesonide equivalent [b.e.]), that continued over to Year 6 (350.2±308.4 µg b.e., -60% compared to baseline [p<0.001]). In the subset of patients reaching Year 6, the proportion receiving ≥2 medications at baseline (93%) decreased to 69% after four years of follow-up and remained rather constant thereafter (data not shown). The percentage receiving ICS and LABA at baseline (100% and 93%) also decreased significantly (75% and 64% at Year 6, p<0.001 both), as did the dose of ICS.

Main effectiveness results for the subset of patients >6 years are available in eTable 4.

Adverse events

Twenty-one of 484 (4.3%) patients experienced at least one AE. These included headache (n=8, 1.7%), unspecific symptoms like malaise, fatigue, asthenia, low-grade fever, myalgia, and/or flu-like syndrome (n=5, 1.0%), injection site pain/reaction (n=4, 0.8%), dizziness/loss of consciousness/vasovagal syncope (n=4, 0.8%), transient urticaria (n=2, 0.4%), anaphylaxis, Burkitt lymphoma, epistaxis, abdominal pain,

immune thrombocytopenia, and impaired wound healing (n=1 [0.2%] each). There were no deaths during omalizumab treatment.

Discontinuations

Overall, 123/484 (25.4%) patients discontinued omalizumab. Discontinuations due to good evolution of disease were the most common (n=99, 20.5%), and occurred for 0.2%, 1.2%, 2.5%, 2.1%, 3.9%, and 6.2% of patients between Years 1-6, and for 21.2% of patients thereafter. Less common reasons were lack of efficacy (n=17, 3.5%), loss to follow-up (n=13, 2.7%), and patient decision (n=3, 0.6%). Seven (1.4%) patients discontinued due to AEs/concomitant disease: malaise (n=2), headache, anaphylaxis, Burkitt lymphoma, abdominal pain and immune thrombocytopenia (n=1 each). Reason was not reported in seven (1.4%) patients. Discontinuations increased with age (≤6 years: 2.1%, >6-12 years: 43.8%, >12 years: 54.1%).

Discussion

To our knowledge, ANCHORS is the first observational study reporting outcomes for up to 6 years of omalizumab in a large cohort of pediatric patients with SPAA. Many patients were still on follow-up at Year 6, allowing for more precise estimates. Moreno-Galarraga et al[11] and Folque et al[12] have reported omalizumab outcomes for a maximum of approximately 6 years, but in 13 and 48 patients respectively.

Our cohort was clearly uncontrolled despite the high medication use, indicated by the number of exacerbations, healthcare encounters, rescue corticosteroids use and QS during the baseline period. In the year after omalizumab initiation, the annual number of MSE was reduced to 1.1. A prospective real-life study by Deschildre et al[19] also noted a significant reduction in severe exacerbations by using a definition similar to our MSE, from 4.4 to 1.3 during the first year of omalizumab. These patients had baseline FEV_1,

MMEF and use of ICS similar to our cohort, while duration of asthma and IgE levels were higher and ICS dose lower.

In our study, children ≤6 years had significantly higher number of MSE than older ones, which may have been the main reason for the off-label treatment with omalizumab. Their improvement in MSE during the first year was more remarkable, but the adjusted change in MSE across age groups and years of follow-up did not show consistent differences. Furthermore, patients >6-12 and >12 years showed a significant improvement of lung function, leading us to believe that improvement is not age-dependent. The lack of significant and consistent improvement in lung function for patients ≤6 years may be due to the comparatively better values at baseline, as disease duration may have been too short to produce a significant decline, and to the smaller number of patients in this subgroup.

For all outcomes, significant improvements occurred during the first year. We did not evaluate earlier time points, but previous studies have found significant amelioration after only 3-6 months of omalizumab.[5,7,11,12] In our case, the improvement was maintained (or even continued) throughout 6 years of follow-up, as reported by Moreno-Galarraga et al[11] and Folque et al.[12] Despite the shorter follow-up, Deschildre et al also observed maintenance of omalizumab benefits for up to two years.[3] Furthermore, in our study, the improvements were accompanied by a progressive and durable gain in disease control. To our knowledge, these are the longest follow-up data for disease control reported in pediatric patients with SPAA, supporting a continued effectiveness of omalizumab without development of tachyphylaxis. The rate of AEs in our cohort was very low, and the most frequent were consistent with the safety profile of omalizumab. Few patients discontinued due to AEs, one of them a Burkitt lymphoma.

Although we cannot rule out a causal relationship, systematic reviews and pooled analysis have not shown increased risk of malignancies with omalizumab.[20–22]

Although this evidence supports the long-term use of omalizumab, an earlier discontinuation may be feasible in a considerable subset of patients. In our study, only 1.4% of patients discontinued omalizumab due to good evolution during the first two years, but the percentage increased to approximately 16.1% after six years of follow-up. Deschildre et al[23] reported a similar percentage after only two years of follow-up, but the baseline number of exacerbations and ICS dose were lower in their cohort, suggesting a better initial disease control.

Our results point at an indirect anti-eosinophilic effect of omalizumab. This was accompanied with a significant reduction in FeNO, also noted in prior studies.[11,24] An elevated eosinophil count increases the risk of asthma exacerbations and, when coupled with an elevated FeNO, is associated to higher asthma morbidity.[25,26] In severe asthma, high eosinophil levels may persist despite high-dose ICS therapy,[27] so our findings are particularly relevant in the population with SPAA.

The requirement for rescue corticosteroids and the use of ICS decreased from the first year. This corticosteroid-sparing effect confirms that reported in previous real-life studies,[12,19,28] and is of major importance in children, as both the exposure to rescue corticosteroids and long-term use of ICS increase the risk of adrenal supression,[29] and ICS have a dose-dependent negative effect on growth.[30] The sparing effect extended to all other asthma medications. The apparent increase from Year 5 in the number of medications and the use of ICS and LABA may be an statistical artifact, as some patients had not reached Year 5 by the time of data collection. Another possible reason would be selection bias, as some patients discontinued omalizumab before Year 5 due to good evolution. In fact, patients who reached Year 6 were already receiving many

treatments at baseline. In these patients, the dose of ICS decreased over time. The growing proportion of asthma control and discontinuations due to good evolution, along with the consistently low number of exacerbations and healthcare encounters, also exclude an upturn in asthma severity over time.

Our study has some limitations. The diagnosis of SPAA based on physicians' criteria may have led to the inclusion of patients with a wide range of disease status. However, baseline characteristics pointed at a general severity of asthma. We pooled data from pre-existing databases which differed in the parameters recorded, time of assessments, and format/units used. In some variables, this required manual categorization and/or conversion of values in order to summarize and analyze them, which may have decreased data granularity. The high number of missings observed in some variables may have biased results (e.g. mild exacerbations were less frequent than MSE, which points at an underestimation). Also, the expected high number of missing values for asthma control obliged us to pool data from various questionnaires, which differed in several aspects. Nevertheless, the conservative approach chosen to analyze asthma control most probably lead to underestimation. We failed to collect some variables that may have influenced our results (e.g., allergen exposure, inhaler technique, treatment adherence). Finally, we cannot exclude some improvement due to surveillance bias, since patients were visited very frequently.

In conclusion, in our large real-life cohort, there was a significant reduction in the number of MSE and a significant improvement in all other clinical parameters assessed during the first year of treatment with omalizumab. The beneficial effect was maintained in the long-term, along with a good safety profile and a positive impact on medication use and healthcare encounters. Our results confirm those of prior

observational studies, and position omalizumab as an effective long-term treatment in patients with SPAA unable to achieve disease control with non-biological treatment.

Acknowledgements

The authors want to thank their families, centers, pediatricians and nurses from the pediatric allergy and pulmonology units participating in the study, as well as patients and their families, for their patience and collaboration during this project.

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441 **Table 1. Demographic and clinical characteristics at omalizumab initiation**

	Effectiveness population (n=426)
Sex (male), n (%)	263 (61.7)
Age (years),	11.1 (2.9)
Range	1.9-17.9
Time from asthma diagnosis (years)[a]	5.5 (3.6)
Time from severe asthma diagnosis (years)[b]	1.4 (2.0)
Total IgE (kU/L)[c]	976.5 (1196.8)
FeNO (ppb)[d]	44.5 (37.5)
FEV_1 (% predicted)[e]	84.6 (18.1)
MMEF (% predicted)[f]	64.9 (37.6)
Absolute eosinophil count (cells/mm^3)[g]	640.1 (447.7)
MSE (annual number)	7.9 (6.6)
Mild exacerbations (annual number)[h]	4.9 (4.1)
Sensitizations, n (%)[i]	
House dust mites	299 (70.2)
Animal dander	150 (35.2)
Alternaria	147 (34.5)
Olive pollen	144 (33.8)
Grass pollen	105 (24.6)
Other pollen	105 (24.6)
Hen's egg	43 (10.1)
Nuts	40 (9.4)
Cow's milk	33 (7.7)
Other foods	50 (11.7)
Cockroach	10 (2.3)
Prior SIT, n (%)[j]	201 (47.2)
Good tolerance to prior SIT[k]	131 (65.2)
Current SIT, n (%)[l]	151 (35.4)
Smoking (passive/active), n (%)	22 (5.2)
Comorbidities, n (%)[i]	
Rhinoconjunctivitis	243 (57.0)
Atopic dermatitis	153 (35.9)
Food allergy	133 (31.2)

	Effectiveness population (n=426)
Eosinophilic esophagitis	38 (8.9)
Overweight/Obesity	30 (7.0)
Other	48 (11.3)

Values given as mean (SD) unless otherwise indicated. [a] Missing for 84 patients. [b] Missing for 83 patients. [c] Missing for 13 patients. [d] Missing for 149 patients. [e] Missing for 12 patients. [f] Missing for 64 patients. [g] Missing for 94 patients. [h] Missing for 152 patients. [i] Each patient may have more than one. [j] Missing for 52 patients. [k] Missing for 2 patients. [l] Missing for 32 patients. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume at first second; MMEF, maximum mid-expiratory flow; ppb, parts per billion; MSE, moderate-to-severe exacerbations; SD, standard deviation; SIT, specific immunotherapy.

Figure 1. Annual evolution of MSE in the total effectiveness population (A) and by age group (B)

Bars and data labels represent the mean value. Whiskers represent the SD. * $p<0.001$ versus baseline from this point onwards. † $p<0.001$ versus baseline in Year 1, $p<0.05$ versus baseline for Years 2 to 4. MSE, moderate-to-severe exacerbations; SD, standard deviation.

Figure 2. Annual evolution of FeNO (A), FEV1 (B) and MMEF (C) (effectiveness population)

Points and labels represent the mean value. Whiskers represent the SD. * $p<0.001$ versus baseline from Year 1 to Year 5; $p=0.001$ at Year 6. † $p<0.001$ versus baseline from this point onwards. FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume at first second; MMEF, maximum mid-expiratory flow; ppb, parts per billion; SD, standard deviation.

Figure 3. Annual evolution of absolute eosinophil count (effectiveness population)

Points and labels represent the mean value. Whiskers represent the SD. * $p<0.001$ versus baseline from this point onwards. SD, standard deviation.

Figure 4. Annual evolution of healthcare encounters (effectiveness population)

Bars and labels represent the mean value. Whiskers represent the SD. * $p<0.001$ versus baseline from this point onwards. † $p<0.001$ versus baseline from Year 1 to Year 5; and $p<0.05$ at Year 6. PICU, pediatric intensive care unit; SD, standard deviation.

Figure 5. Annual evolution in the number (A) and type (B) of chronic concomitant medications (effectiveness population)

* $p<0.001$ versus baseline from this point onwards. † $p<0.001$ at Year 1 and Year 2, $p<0.05$ at Year 3. p not estimable from Year 4 onwards. ‡ $p<0.001$ at Years 1,2 and 5; $p<0.05$ at Year 3 and Year 4. Not significant at Year 6. ICS, inhaled corticosteroids; LABAs, long-acting beta-agonists; NA, not available.

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