

Article

Clinical experience with anti-IgE monoclonal antibody (Omalizumab) in paediatric severe allergic asthma – a Romanian perspective.

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Abstract

Background: Asthma is the most common chronic disease affecting children and altering their quality of life. The severity of asthma is often modulated by immunoglobulin E (IgE)-mediated allergen sensitization and is associated with comorbid allergic diseases. Omalizumab is a humanized monoclonal antibody anti-IgE, the first biological therapy approved to treat patients aged ≥ 6 years with severe allergic asthma. The primary objective of our study was to investigate the efficacy and safety of Omalizumab in Romanian paediatric patients with severe allergic asthma.

Methods: In this observational real-life study, 12 children aged 6 to 18 years, (mean age 12.4 years) with severe allergic asthma received Omalizumab as an add-on treatment. The levels of asthma control, exacerbations, lung function and adverse events were evaluated at baseline and after the first year of treatment.

Results: We noticed general improvements in total asthma symptom scores and the rate of exacerbation of severe asthma. Omalizumab increased the initial variables of lung function, and no serious adverse reactions were reported. FEV1 improved statistically significant after one year of treatment with Omalizumab, [Δ FEV1 (% pred.) =18.3, and similarly, Δ MEF50 (%) = 25.8]. The mean severe exacerbation rates due to asthma decreased from 4.1 (2.8 SD) to 1.15 (0.78 SD) during the treatment year ($p < 0.0001$) with Omalizumab.

Conclusions: Treatment with Omalizumab can be an effective and safe therapeutic option for Romanian children with severe allergic asthma, providing clinically relevant information on asthma control and exacerbation rate in children and adolescents. The results highlighted the effect of Omalizumab in young patients, starting from the first year of treatment.

Keywords: allergic severe asthma; anti-IgE; Omalizumab; observational study; children

1. Introduction

Asthma is defined as a chronic inflammatory disease of the lower respiratory tract affecting between 1 and 18% of the general population, most of which started in early childhood [1-3]. On average, between 10 and 12 % of children under the age of 6 or 7 years of age and 14 % of adolescents between the ages of 7 and 14, of the global population suffer from asthma [4,5]. Up to 90% of childhood asthma has an allergic background and is associated with personal or family history of allergic diseases such as allergic rhinitis, atopic dermatitis, or food allergy. Allergic children have an increased risk of developing asthma by 30% [6,7].

According to guidelines, asthma is considered severe if needs high doses of controller therapy - step 4-5 GINA (Global INitiative for Asthma) guideline to be controlled or remains uncontrolled despite correct administration of therapy and treatment of contributory factors or, worsening asthma at step-down of doses of treatment [1]. The severity of asthma is evaluated according to the guidelines criteria such as the frequency of daily/night episodes, the level of intensity and frequency of exacerbations, its duration, the presence/absence of symptoms between acute events and the frequency of use of short-acting inhaled β_2 agonists. Following a systematic assessment to optimize asthma control [6-8], approximately 5–15% of the asthmatics remain to have severe asthma [9], which is associated with increased morbidity and mortality. The incidence of severe pediatric asthma is about 2.5% of all children with asthma. It accounts for approximately half of all health resources for pediatric asthma and is associated with a higher risk of exacerbation, an increased risk of mortality and onset of chronic obstructive pulmonary disease in adulthood [8,9]. Therefore, safe and effective treatment options are considered necessary for children with uncontrolled severe asthma [10].

The discovery of immunoglobulin E (IgE) as a key player in allergic diseases and the association of higher mean levels of plasma IgE with severe asthma [11] underscores the rationale for developing safe and effective targeted anti-IgE therapy, which has become an important therapeutic option in adult and pediatric patients with severe uncontrolled allergic asthma [12-14].

Asthma is a mixed syndrome combining several immunological subtypes [15-17], of which the best described is the allergic phenotype.

The development of allergic asthma mainly involves the synthesis of IgE antibodies against aeroallergens, such as mold, cat and dog dander, mites, etc. The ability to generate high levels of specific IgE antibodies is favoured by the genetic susceptibility for such a response and is accompanied by an unbalanced ratio of T-helper 1 (Th-1) / T-helper 2 (Th-2) lymphocytes. Characteristic of allergic inflammation, higher expression of Th-2 cytokines than Th-1 cytokines results in the production of interleukin (IL): IL-4, IL-5, IL-6, IL-9 and IL-13, acting as inflammation allergic mediators [18,19].

The high incidence of allergy in pediatric asthma and the increased values of serum total IgE usually encountered in severe forms are reliable reasons for the use of anti-IgE therapy in children. Omalizumab, a subcutaneously administered humanized anti-IgE monoclonal antibody, was approved as add-on therapy for patients with moderate to severe persistent allergic asthma uncontrolled despite daily high-dose ICS plus inhaled LABA treatment or other controller treatment, who have a positive skin prick test response or in vitro reactivity to a perennial aeroallergen [20-22]. In that respect, owing to the central role of IgE antibody in the pathophysiology of allergic disorders, Omalizumab is the first biological agent authorized for the treatment of severe allergic asthma in children. Omalizumab is a murine (95%) humanized recombinant IgG1 monoclonal antibody. Its mechanism of action consists in selectively binding of free IgE and inhibition of the interaction of IgE with the high-affinity IgE receptor (Fc ϵ RI) localized mast cells and basophils, therefore disrupting the allergic cascade and influencing the entire inflammatory process through reduction of inflammatory cells activation and decrease of the release of pro-inflammatory factors (early phase of allergic response) [5, 22]. Besides, by attaching to Fc ϵ RII/CD23 receptors on B cells, Omalizumab affects their antigen-presenting role. This action modulates the dialogue between B cells and T cells, induces IgE receptors downregulation by significant ($\leq 99\%$) and rapid

reductions of free IgE levels, therefore blocking Th2 amplification of the inflammatory response. Prevention by Omalizumab of degranulation of the mast cells and basophils reduces the inflammatory response in the upper and lower airways in all phases of the allergic reaction, enabling also the modulation of the process of airway remodelling [6], thereby effectively improving control of symptoms and progression of asthma [23-24].

Omalizumab is approved for the treatment of children (6-<12 years) and adults and adolescents (>12 years) with severe allergic asthma (mediated by IgE) in Romania, according to the European Medicines Agency [23]. As outlined in a wide range of clinical trials and real-life studies, Omalizumab has been widely demonstrated to be clinically effective and safe treatment in adults and children, reducing asthma exacerbations rates and the doses of corticosteroids able to control asthma symptoms, improving the pulmonary function tests and the quality-of-life scores [20].

Our study aims to evaluate for the first time to our knowledge, the effect of Omalizumab in paediatric severe allergic asthma to confirm whether the outcome of treatment in a Romanian population is consistent with findings in previously published data.

2. Materials and Methods

The 1-year real-life observational study conducted in a single center of "M.S. Curie", Children's Emergency Clinical Hospital of Bucharest, Romania, included all pediatric patients aged 6 to 18 who met the criteria for severe allergic asthma and started additional therapy with Omalizumab between 2013 and 2019.

To identify children with severe allergic asthma under biological treatment with anti-immunoglobulin E monoclonal antibodies (Omalizumab), we have searched the database of the Department of Allergy-Clinical Immunology and Pediatric Pneumology of the "M.S. Curie" Children's Emergency Clinical Hospital of Bucharest. Severe asthma in children and adolescents has been defined according to current guidelines [1] as asthma requiring stage 4 or 5 of treatment to get control of symptoms or remain uncontrolled despite the high level of optimised treatment.

In Romania, Omalizumab is an authorized-on treatment in severe allergic asthma, in line with eligibility criteria and Summary of Product Characteristics approved by the National Agency for Medicines and Medical Devices of Romania (NAMMDR) and the European Medicines Agency (EMA). The doses and frequency of administration of omalizumab are established as recommended, adapted to serum total IgE levels and the patient's body weight. Those children who have a positive skin test or in vitro reactivity (blood test) to a perennial aeroallergen and who have frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS plus LABA, with lung function parameters lower than 80% of normal for patients aged 12 years or over [25-27].

Baseline characteristics of study participants were collected from patient records, consisting of demographic data, asthma-related clinical history (age at asthma diagnosis, inhaled corticosteroid (ICS) doses and medications used, visits to the emergency department, hospitalizations/or intensive care unit admissions for asthma ever) and asthma severity, history of exacerbations requiring the use of systemic corticosteroids (we considered clinically significant an exacerbations that required at least 3 days of systemic corticosteroids), total IgE levels, circulating eosinophil count and allergic sensitization by skin prick test and/or specific IgE to

common perennial and seasonal allergens (Dermatophagoides pteronys-sinus, Dermatophagoides farinae, trees, grasses and weeds pollens, moulds, cat and dog danders), comorbidity data (allergic rhinitis, atopic dermatitis).

Due to the low incidence of severe allergic asthma in children and the small number of cases identified in our database, we decided to evaluate the asthma response to treatment with Omalizumab, analyzing commonly used parameters, baseline and after the first year of treatment. Exploratory efficacy results included changes in 1) asthma control level; 2) severe exacerbations rate and healthcare use; 3) lung function over the first year of treatment [mean morning forced expiratory volume (FEV1) and forced expiratory flow rate at 50% of forced vital capacity (MEF50)]; 4) ICS doses as maintenance therapy. Safety assessments consisted of the recording of adverse events recorded during one year of doses administered.

The responsiveness to Omalizumab was evaluated using criteria as the achievement of asthma control over the year of treatment, reduction in severe exacerbation rate and healthcare use in comparison with that observed before omalizumab therapy, reduction in maintaining treatment doses, and improvement of the lung function over the year of treatment.

The statistical analysis was performed using SPSS IBM. $p < 0.05$ value was attributed to statistical significance.

Ethics

All the parents gave written informed consent for their children participation and follow-up. The research protocol number 31211/06.08.2021, for this observational study, was previously approved by our institutional review board, of the Scientific research ethics committee of the "M.S. Curie" Children's Emergency Clinical Hospital of Bucharest.

3. Results

A group of 12 patients between 6 and 18 years of age (mean age 12.4 years, standard deviation (SD) - 4.1 years) was selected, confirming severe allergic asthma for which additional treatment with Omalizumab was initiated between 2013 and 2019. The group was included in a retrospective observational study and all data were evaluated at initiation and after the first year of treatment.

The baseline characteristics of the study participants are detailed in Table I. The group consisted of 3 girls (25%) and 9 boys (75%), and the mean age at asthma diagnosis was 6.5 years with a SD of 3.77 years. Personal history of atopic dermatitis was observed in 9 patients (75%) and allergic rhinitis was recorded in 10 patients (83.3%). A familial history of atopy was present in 8 patients (66.6%). All patients had allergic sensitisation to at least one perennial allergen relevant to asthma symptoms, while 11 patients (91.7%) had allergic sensitisation to multiple inhaled allergens.

Table I. Baseline demographic and clinical parameters of enrolled patients.

Characteristics	Patients n = 12
Age (years), mean (SD)	12.4 (4.1)
Sex, n (%)	
Male	9 (75)
Female	3 (25)
Age at diagnosis (years), mean (SD)	6.5 (3.77)
Personal history of atopy, n (%)	
Atopic dermatitis	9 (75)
Allergic rhinitis	10 (83.3)
Familial history of atopy/asthma, n (%)	
+	8 (66.7)
–	4 (33.3)
Total serum IgE (IU/mL), median (range)	1102.6 (371.7)
Eosinophil number, median (range) ($\times 10^3/\text{mm}^3$)	0.589 (0.1–0.99)
Allergic sensitization n, (%)	
Polysensitization	11 (91.7%)
Monosensitization	1 (8.3%)
FEV ₁ (% of predicted), mean (SD)	86.74 (16.01)
MEF _{50%} (% of predicted), mean (SD)	76.30 (27.22)
Number of asthma exacerbations in the previous year, before starting Omalizumab, mean (SD)	4.1 (2.8)
ICS dose at baseline ($\mu\text{g}/\text{day}$, fluticasone propionate equivalent)	
Mean (SD)	469.7 (199.84)
Median (range)	500 (250–1000)
Asthma long-term control medications at baseline, n (%)	
Leukotriene receptor antagonist	11 (91.7)
Long-acting β_2 -agonist	8 (66.7)
Oral corticosteroid	0 (100)
Level of asthma control before treatment with Omalizumab, n (%)	
Controlled	0 (0)
Partial controlled	5 (41.7)
Uncontrolled	7 (58.3)
Treatment with Omalizumab, years, median (SD)	3 (2.094)

The mean dose of ICS (FP equivalent) was 468.7 $\mu\text{g}/\text{day}$, and most patients (97.4%) used LTRA and LABA, respectively. Patients had experienced an average of 4.1 exacerbations of asthma (SD = 2.8) and, at inclusion, most had daily activity limitations. The level of asthma control at the time of treatment decision with omalizumab was classified according to the GINA guideline recommendations, i.e., controlled, partially controlled and uncontrolled asthma.

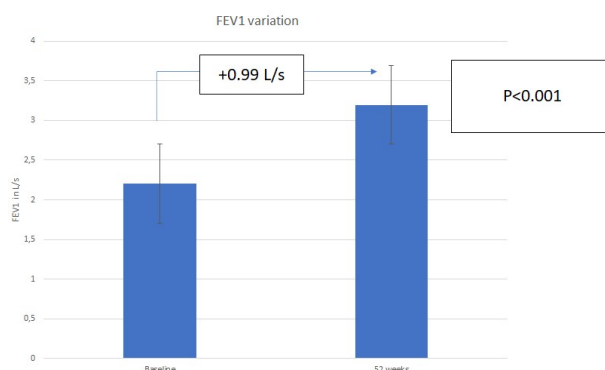
According to the GINA criteria, asthma is well controlled if there are daytime symptoms not more than two or less per week; limitation of activities - none; nocturnal symptoms/awakening - none; need for relief/rescue treatment twice or less per week. Asthma is partially controlled if 1-2 of these criteria are present, not controlled if 3-4 of these criteria are met[1]. Thus, 5 patients in the study group (41.7%) were classified as partially controlled disease carriers, while in 7 patients (58.3%), the disease was not controlled despite high doses of controlled drugs.

In order to compare the results of treatment with omalizumab in the study group and to monitor asthma control, we used validated asthma questionnaires (asthma control test - ACT). Thus, the child asthma control test (C-ACT) was clearly improved in the first year of treatment. Asthma control levels improved to be controlled in 75% of cases, partially controlled in 25% of cases and uncontrolled in 0% of cases after the first year of treatment.

A decrease in the mean rate of severe exacerbations was observed: prior to treatment with omalizumab, 100% of patients had more than 2 asthma exacerbations in the previous year, while, after one year of treatment, 16.7% of patients had more than two asthma exacerbations induced by exercise and none had viral-induced exacerbations. The mean rate of severe exacerbations decreased from 4.1 (2.8 SD) per patient in the previous year to 1.15 (0.78 SD) in the course of the treatment year ($p < 0.0001$).

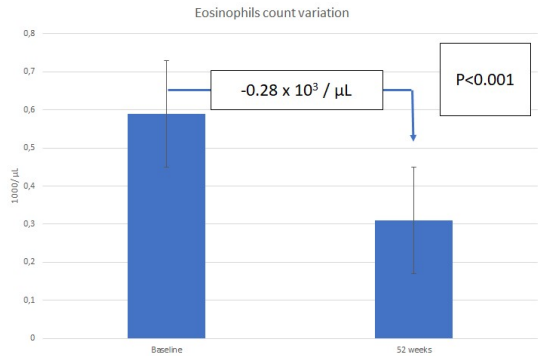
Pulmonary function test revealed a decrease in the values of FEV1 (mean value = 86.74%) and MEF50 (mean value = 76.30%) prior to treatment, which improved after one year of treatment with Omalizumab (mean FEV1 = 105.03%, mean MEF50 = 102.13%). The absolute FEV1 showed similar results with mean improvements of 0.99 L after the first year of Omalizumab treatment (Fig I).

Figure I. FEV1 variation after 52 weeks of treatment with Omalizumab.



Mean (SD) reductions in eosinophil counts of -280 cells/mL (166) were noted in our group of patients after one year of treatment with Omalizumab.

Figure II. Circulating eosinophil count variation after 52 weeks of treatment with Omalizumab.



A reduction in the maintenance dose of the medication was possible in 9 patients (75%), and the ICS was reduced in all patients. Mean ICS dose at 12 months has decreased in the equivalent of 275 μ g fluticasone propionate. (See Table II).

Recorded safety data have also been collected. All reactions were mild and appeared after the first dose of medication, with the most frequent AEs being pain at the injection site (12), flu-like symptoms (5), headache (3). No adverse reaction resulted in discontinuation of therapy, and no anaphylaxis reports were found in the study group during either the first year or for all years of treatment with omalizumab.

Table.2. The outcome of treatment with Omalizumab.

Parameter	T0	T1
Eosinophil number, median ($\times 10^3/\text{mm}^3$)	0.589	0.309
FEV ₁ (% of predicted), mean	86.74	105.03
MEF _{50%} (% of predicted), mean	76.30	102.13
Patients with ≥ 2 asthma exacerbations, n (%)	12 (100)	2 (16.7)
Number of asthma exacerbations after the first year of treatment with Omalizumab, mean (SD)	4.1 (2.8 SD)	1.15 (0.78 SD)
Level of asthma control before treatment with Omalizumab, n (%)		
Well-controlled	0 (0)	9 (75)
Partial controlled	5 (41.7)	3 (25)
Uncontrolled	7 (58.3)	0
Decrease of maintenance doses of treatment, n (%)	-	9 (75)

4. Discussion

We have reported a retrospective observational survey of 12 paediatric patients with severe allergic asthma who have demonstrated that they benefit from additional anti-IgE monoclonal antibodies (Omalizumab) therapy for high-level maintenance treatment.

In pediatric asthma, control of symptoms can be achieved in most cases by low to medium doses of ICS plus one or more controlling drugs. In poorly controlled cases, the cause is often related to technical mistreatments or errors in the administration of control drugs. Although less frequently than in adults, there are children with severe allergic asthma whose disease remains uncontrolled despite high doses of standard medications. In clinical studies, complementary treatment with IgE monoclonal antibodies was clinically effective and a safety profile in patients with severe asthma [28], chronic urticaria [9,29] and, more recently, in patients with chronic rhinosinusitis with nasal polyposis [30-31]. Absorption of omalizumab in systemic circulation is relatively slow, with peak serum concentrations achieved after an average of 7-8 days. This monoclonal anti-IgE antibody demonstrates linear pharmacokinetics in approved dosing regimens. The process of clearance of IgG, as well as specific and complex binding formation with IgE, are involved in the clearance of omalizumab. The average half-life is 26 days [8]

Reduction of serum IgE is observed in a few hours since administration and the number of high-affinity IgE receptors diminishes following 8 - 12 weeks of treatment, with peak levels apparent 7-8 days after single-dose administration and steady-state levels reached in the serum in 14-28 days following multiple-dose administration [25].

Observational studies provide real-life data and could bring valuable information that might differ from those obtained in clinical trials. To our knowledge, this is the first observational study investigating the efficacy of Omalizumab as add-on therapy to high-level maintenance treatment in Romanian pediatric patients with severe persistent allergic asthma.

Over one year of treatment, the rate of clinically significant asthma exacerbations is a good efficacy of treatment endpoint evaluated in clinical studies. Three pivotal Phase III clinical trials in patients with moderate-to-severe asthma were performed in the USA and Europe on a population of 1071 ICS-dependent symptomatic adolescents and adults, and 334 pediatric patients (aged 6–12 years), followed by other 25 trials, enrolling a total of 6382 patients with uncontrolled allergic asthma analysed a Cochrane meta-analysis, resulted all in effective reduction of asthma exacerbations by omalizumab treatment [32-33]. Recent systematic reviews of the results of multiple randomized, blinded, placebo-controlled phase III studies involving children 6 to 11 years of age [34] or adults and children over 6 years old age [35,36] resulted also in effective improvement in asthma control by reducing asthma exacerbations, hospital admissions, acute asthma attacks and the related need of oral corticosteroid (OCS) in severe asthmatic children. In our study, we observed a statistically significant reduction of the rate of exacerbations after the first year of treatment (mean rate of severe exacerbations decreased from 4.1 (2.8 SD) per patient during the previous year to 1.15 (0.78 SD) during the first year of treatment ($p<0.0001$)) and decrease of number of patients who developed asthma exacerbation, with less asthma acute symptoms induced by exercise (2 from 12

patients) and no exacerbations induced by viral respiratory infections during the first year of treatment with Omalizumab. This result is in concordance with those reported in other observational studies: 72% reduction of exacerbations over one year and two years of treatment (mean, 1.25 vs 4.4, $P < 0.0001$), reported in an observational study involving 104 patients (6-18 years old) with severe allergic, partially/poorly controlled asthma, by Deschildre et al. [37,38]; 91% reduction of asthma exacerbation (mean, 0.8 vs 7.2; $P < 0.0001$) reported after one year of Omalizumab in a cohort of 47 patients with severe allergic asthma on Omalizumab: (6-21 years old,) by Licari et al. [20]; hospitalization decreased by 70% ($P = 0.02$) after 6 months of treatment with Omalizumab in a cohort of 14 pediatric patients (6-18 years of age) with severe allergic asthma, reported by Pitrez et al [39]; 69.2% reduction of frequency of exacerbations in a group of 38 Japanese children (6-15 years old) with severe persistent allergic asthma receiving Omalizumab [40]. It is important to note that the degree of improvement of exacerbations rate has been correlated in clinical trials with the number of exacerbations before starting the treatment with Omalizumab, baseline pulmonary function or eosinophil count, with different results in different studies, improvements being greater in children with more severe subtypes [41]. An elevated eosinophil count is associated with higher risk of asthma exacerbations [1, 36]. It is important to note that 91.7% of the patients in our study were polysensitized, a trait that, together with the increase in the number of circulating eosinophils, high levels of total IgE, are parameters related to the severity of asthma and it was suggested that these characteristics may be relevant for a subpopulation of serious, true, highly allergic asthma, with a good response to Omalizumab (37). In our study group, we observed a slight decrease in the mean counts of absolute eosinophil cells after one year of treatment. The effect seems to be correlated with the duration of treatment, the lowest value compared to baseline was recently reported in a study after 6 years of treatment [36]. The pulmonary function evaluated by both large (FEV1) and small (MEF50) airway functional parameters, improved over one year of treatment with Omalizumab. As has been observed in other studies, the mean baseline FEV1 was $> 80\%$ also in our patients, and this is due to the early age of patients whose lung function was not already reduced as we expect in severe asthma in adults [14]. Although the increase in pulmonary parameters may not be clinically relevant, it is discussed in the literature as a useful parameter for assessing the therapeutic effect of a specific treatment, since severe forms of asthma in children have been reported to decrease pulmonary function after long-term follow-up [41].

The level of asthma control, another important measure of treatment effectiveness in asthma, has evolved towards improvement (75% controlled patients, 25% partially controlled, none controlled after the first year of treatment, versus 41.7% partially controlled, 58.3% not controlled before additional therapy with Omalizumab) in our study similar to data previously published in other observational studies [14,42]. A dose reduction of controlled medication with the maintenance of control of asthma symptoms was possible in 9 patients (75%) in our group after the first year of anti-IgE treatment.

As for the safety of this treatment, all patients in our group had at least one adverse event during the treatment, but of mild severity. The most common adverse reactions reported were transient localised reactions and local pain [14,42].

The good safety profile of treatment with omalizumab in asthmatic children was evident in clinical and observational studies addressing concerns about the potential association of omalizumab with hypersensitivity adverse reactions.

In this regard, it should be noted that no cases of anaphylaxis have been reported in children, compared to the risk of anaphylaxis of 0.1 to 0.2% reported in adults and adolescents [43,44].

The major limitation of this study is the limited number of patients. Our goal is to enrol new patients and continue follow-up of patients recruited beyond one year after administration of omalizumab treatment.

The main strength of this article is that it presents the first Romanian observational study reporting the outcome of children with severe allergic asthma who received Omalizumab. The results confirmed that Omalizumab improved asthma control, reduced the rate of exacerbations and was well tolerated over one year of treatment.

5. Conclusions

Understanding the benefits of omalizumab treatment and the importance of adherence in the pediatric population may provide insights that may guide the management of omalizumab in patients with asthma treated with this therapy.

In the Romanian pediatric population, one year of Omalizumab therapy improved control of symptoms and lung function and was correlated with a marked reduction in asthma exacerbations caused by viral infections or by exercise and reduced doses of controller medication. Focusing on studies that have reported results in the 24-36 month time window or at 36 months and beyond, there is compelling evidence to infer the long-term efficacy of Omalizumab in the management of severe allergic asthma. In conclusion, omalizumab represents a pivotal therapeutic option for severe allergic asthma in children who remain uncontrolled despite high doses of ICS and other controller drugs. More long-term follow-up studies are needed to confirm these promising results. Data collected through observational real-life studies complete and highlight the efficacy and safety profile of the treatment with Omalizumab in paediatric patients.

Author Contributions: Conceptualization, ECB, MDI. and RSB; methodology, ECB, MB, CGC; software, ECB, CP; validation, ECB, MDI, MB, RSB, CGC, CLT; formal analysis, ECB, MDI; investigation, MB, ECB; resources, ECB, MDI; data curation, ECB, CP; writing—original draft preparation, ECB; writing—review and editing, ECB, MDI, CP; visualization, MB, CGC, CLT; supervision, ECB, MDI, MB; project administration, ECB. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the

Declaration of Helsinki and approved by the Ethics Committee "M.S.CURIE", CHILDREN'S EMERGENCY CLINICAL HOSPITAL OF BUCHAREST, ROMANIA.

Informed Consent Statement: Informed consent was obtained from all parents of children involved in the study.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors ECB, MDI, RSB, have received lecture and meeting fees from Novartis. ECB has received consultancy/advisory board fees and grants from Novartis. The other authors declared no potential conflicts of interest.

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