



Severe asthma phenotypes in patients controlled with omalizumab: A real-world study

Paloma Campo^a, Gregorio Soto Campos^{b,*}, Marina Blanco Aparicio^c, Ana Moreira Jorge^d, Héctor Manuel González Expósito^e, Santiago Quirce^{f,g}, Ignacio Dávila^{h,i}

^a Allergy Unit, IBIMA-Regional University Hospital of Málaga, ARADyAL, Málaga, Spain

^b Pneumology and Allergy Unit. Hospital Universitario de Jerez, Cádiz, Spain

^c Pneumology Service, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

^d Novartis Farmacéutica, Barcelona, Spain

^e Pneumology Service, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

^f Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

^g CIBER de Enfermedades Respiratorias, CIBERES, Madrid, Spain

^h Allergy Service, University Hospital of Salamanca and Institute for Biomedical Research of Salamanca (IBSAL), Salamanca, Spain

ⁱ Biomedical and Diagnosis Science Department, Salamanca University School of Medicine, Salamanca, Spain

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ABSTRACT

Background: The appropriate identification of asthma phenotypes of responders to omalizumab would optimize the selection of treatment.

Objective: To describe the most frequent clinical phenotypes in patients with severe asthma responding to omalizumab and their clinical and pulmonary function improvement.

Methods: This was an observational, retrospective, multicenter study. Adult patients with severe asthma, who achieved good control after the first year of treatment with omalizumab were included. Omalizumab was prescribed according to clinical routine practice. Responders were assigned to one pre-established phenotype based on the most predominant one before they had started treatment with omalizumab, all according to the physician's criteria. Data about asthma symptoms, number of non-severe asthma exacerbations, medication intake (inhaled and oral corticosteroids and rescue medication), lung function, high fractional exhaled nitric oxide (FeNO) and peripheral eosinophils counts were recorded.

Results: Among the 345 patients included, the main phenotypes were severe asthma with frequent exacerbations (29.9%), early-onset allergic asthma (23.8%), severe steroid-dependent asthma (18.8%), and severe eosinophilic asthma (13.6%). Clinical and respiratory changes observed after first year of treatment with omalizumab included: reduction in asthma symptoms, reduction in the use and dose of corticosteroids and need for rescue therapy, improvement of pulmonary function, reduction in the number of episodes of non-severe asthma exacerbations regardless of the duration of severe disease since the diagnosis. Increased blood levels of peripheral eosinophils and high FeNO levels were found at baseline.

Conclusion: Several heterogeneous severe asthma phenotypes were observed as good responders to omalizumab.

1. Introduction

Asthma is a heterogeneous disease, usually characterized by chronic

airway inflammation, with over 350 million affected individuals throughout the world [1]. Asthma is a growing serious global health problem affecting all age groups, and it is expected that 400 million

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AEMPS, Spanish Agency of Medicines and Medical Devices; ATS, American Thoracic Society; ECRHS-I, European Community Respiratory Health Survey; ERS, European Respiratory Society; FeNO, Fractional exhaled nitric oxide; FEV₁, Forced expiratory volume in 1 s; GEMA, Spanish Guidelines on the Management of Asthma; LABA, Long-acting β_2 -agonist; PEF, Peak expiratory flow; QoL, Quality of life; Q1, First quartile; Q3, Third quartile; SD, Standard deviation.

* Corresponding author. Pneumology and Allergy Unit. Hospital Universitario de Jerez, Cádiz, Spain.

E-mail addresses: campomozo@gmail.com (P. Campo), josesoto@separ.es (G. Soto Campos), mba@mundo-r.com (M.B. Aparicio), ana.moreirajorge@novartis.com (A.M. Jorge), hectorbrezo@gmail.com (H.M. González Expósito), squirce@gmail.com (S. Quirce), ldg@usal.es (I. Dávila).

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people worldwide will suffer from asthma by 2025 [1–5]. In accordance with these data, the European Community Respiratory Health Survey (ECRHS-I) showed that the prevalence of asthma increased from 2.1% to 6% in the five Spanish regions that participated in the survey [4].

Following clinical guidelines, asthma severity is assessed according to the level of treatment required to achieve and maintain asthma control [6]. Consequently, severe asthma has been defined as asthma that requires treatment with high dose inhaled glucocorticoids plus a second controller and/or systemic glucocorticoids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy [7]. It is estimated that about 4% of patients with asthma have severe uncontrolled asthma, consuming more than 50% of health costs associated to the disease [8–10].

The impact of severe asthma on patient's quality of life (QoL) is also substantial, as the percentage of severe asthmatic patients achieving a good control of the disease is quite low [11,12]. Patients with severe asthma present high variety of signs and symptoms, physiological changes, and airway inflammation, that severe asthma is not a single disease, but a condition encompassing different phenotypes and endotypes. In addition, patients with asthma do not respond uniformly to asthma medications, particularly to glucocorticoids and other anti-inflammatory drugs. In this regard, although the majority of asthmatic patients improve with inhaled corticosteroids, asthma control remains suboptimal, with 50% of patients experiencing at least one asthma exacerbation per year [13].

Recognizable clusters of demographic, clinical and/or pathophysiological characteristics have been previously described [7,14–16]. There is increasing recognition of phenotypic heterogeneity in patients with asthma, particularly among patients with severe asthma.

Moore et al. as a part of the Severe Asthma Research Program (SARP) identified various clusters of possible phenotypes of severe asthma based on age of onset of asthma, lung function, use of controller medications, health care utilization, obesity, use of oral corticosteroids, frequency of exacerbations, extent of airflow obstruction and airway responsiveness [14]. Various other factors including patient history, clinical symptoms, co-morbidities, eosinophil counts and positive allergen test play important roles in establishing asthma phenotypes [14–16]. The European Respiratory Society/American Thoracic Society (ERS/ATS) work group published a severe asthma phenotype proposal in 2014 [7]. These, and the phenotypes suggested by the Spanish Society of Allergology and Clinical Immunology (SEAIC) [17] have been used in this study, also taking into account the therapeutic response to omalizumab. Nevertheless, there are currently no well-defined and widely accepted asthma phenotypes that correlate well with specific pathological processes or responses to treatments. A better knowledge of asthma phenotypes will contribute to optimize treatment selection [11,15,18].

Omalizumab a humanized, recombinant monoclonal anti-IgE antibody first received approval in the US (2003) [19] for moderate-to-severe allergic asthma followed by its approval for severe allergic asthma in Europe (2005) [20]. It is indicated for patients above 6 years of age with persistent uncontrolled asthma and a positive skin test or *in vitro* reactivity to a perennial aeroallergen. Omalizumab binds to free IgE and interrupts the allergic cascade by inhibiting IgE from binding to FcεRI receptors on mast cells, antigen-presenting cells, and basophils preventing IgE cross-linking, limiting mast cell degranulation, and minimizing the release of mediators in the early- and late phase of allergen response [21]. Furthermore, omalizumab plays an important role in reducing exacerbations by modulating type 2 cytokine production and inhibiting T2 inflammation [22]. A meta-analysis of omalizumab in severe asthma indicated a corticosteroid-sparing effect and a reduction in the frequency of asthma exacerbations [23].

After more than a decade of clinical experience with omalizumab, real-world data as well as results from a large number of randomized controlled clinical trials are available [24–27]. Although clinical trials have significantly contributed to our understanding of the efficacy and safety of omalizumab, the strict predefined eligibility criteria required

for such trials mean that participants do not reflect real-world patients, who often have significant comorbidities and are non-compliant [28]. Therefore, the evaluation of clinical outcomes in the real-world is of utmost importance in order to corroborate the findings from clinical trials and to comprehensively understand the treatment responses of asthma patients.

Our main objective was to describe the most frequent phenotypes of patients with uncontrolled severe disease, who achieved good control of asthma during the first year of treatment with omalizumab. Good control was defined according to the Spanish Guidelines on the Management of Asthma (GEMA) [29].

2. Methods

2.1. Study design and subjects

FENOMA (*FEN*otipos of *as*MA) was an observational, retrospective, multicenter real-life study, carried out in 69 Spanish centers. Between February 2015 and June 2016, medical records were reviewed in order to identify patients ≥ 18 years with severe persistent asthma (step 5 or 6 of maintenance therapy for adult asthma according to the GEMA criteria) [29] who had started treatment with omalizumab (as per routine practice) between 1st January 2010 and 31st December 2013, and who had achieved good control of the disease after finishing the first year of treatment with omalizumab. Good control of the disease was defined following GEMA criteria: no diurnal asthma symptoms or asthma symptoms ≤ 2 days/week, no nocturnal asthma symptoms, no need for rescue medication or ≤ 2 days/week, normal pulmonary function (forced expiratory volume in 1 s (FEV₁) $\geq 80\%$ of the theoretical value/peak expiratory flow (PEF) $> 80\%$ of patient personal best), no activity limitation, and non-severe asthma exacerbation during this period. Patients who had participated in any clinical trial during the observational period were excluded. Data for the study were obtained from the medical records of the included patients. When available, data from Asthma Control Test (ACT) were also collected [30,31].

2.2. Study variables

The clinical data of the patients corresponding to the year before the start of treatment with omalizumab and the first data after one year of treatment with omalizumab were recorded. The main objectives were: (i) to classify patients with severe asthma who had responded to omalizumab in different clinical asthma phenotypes (ii) to describe the distribution of these phenotypes. Phenotypes were selected among those which were the most representative of routine clinical practice, and they were defined following the 2014 ERS/ATS consensus of severe asthma [7].

Physicians, according to their own criterion, assigned each patient to the best predominant defining phenotype, just before they had initiated treatment with omalizumab, according to the protocol definitions given.

The protocol phenotypes and their definitions were: (i) early-onset allergic asthma [onset before 12 years, high levels of IgE, positive skin test (immediate hypersensitivity against a battery of environmental aeroallergens and their specific IgE values) and high fractional exhaled nitric oxide (FeNO)]; (ii) severe asthma with frequent exacerbations (more than 3 exacerbations during the previous year, peripheral eosinophilia and poor response to inhaled corticosteroids and/or oral corticosteroids); (iii) asthma with fixed air-flow obstruction (FEV₁ $< 80\%$ and reversibility $< 20\%$; it could include current smokers and former smokers); (iv) severe steroid-dependent asthma (absence of response to inhaled and/or oral corticosteroids, history of severe exacerbations related to respiratory infections); (v) early (< 12 years) and late (≥ 12 years) onset severe eosinophilic asthma [peripheral eosinophilia and sputum (if available), history of frequent exacerbations with good response to oral corticosteroids and high FeNO]; and (vi) severe asthma in obese women (late onset of asthma, normal IgE levels, FeNO and

eosinophils, with moderate response to corticosteroids).

The secondary objective of the study was to describe the clinical improvement of the patients after the first year of treatment with omalizumab.

With this purpose, the following variables were considered: improvement of diurnal symptoms; reduction of oral corticosteroids intake as maintenance therapy or for asthma exacerbations, use of inhaled corticosteroids, or need of rescue therapy (short-acting β_2 -agonists); improvement of pulmonary function (FEV₁); reduction of the number of non-severe asthma episodes; and reduction of the number of days of school or workplace absenteeism.

The following information about patients' status was collected from the medical records: demographic data; anthropometric data; smoking habits (Never, Former (≥ 1 year), Current); relevant comorbidities for asthma (allergic rhinitis, sinus polyposis, atopic dermatitis); family history of allergy; ACT; FeNO; total serum IgE levels; blood eosinophils levels; skin prick tests; number and type of asthma exacerbations (severe and non-severe). Non-severe asthma exacerbations were exacerbations that did not require oral corticosteroids, emergency assistance or hospitalization.

2.3. Ethics

The study was classified by The Spanish Agency of Medicines and Medical Devices (AEMPS) and approved by the Independent Ethics Committee of the Hospital Universitari Germans Trias i Pujol. The study was conducted according to Good Clinical Practice (International Conference of Harmonization) guidelines [32], and following the local regulation, including privacy laws.

2.4. Statistical analysis

Continuous variables are presented as mean, SD and 95% CI, or median and quartile 1 (Q1) and quartile 3 (Q3), as applicable. Categorical variables are reported by using frequencies and percentages. Descriptive statistics were calculated for demographic and clinical characteristics. For statistical comparisons, the following tests were used, as applicable: Chi-square test, Fisher's exact test, paired t-test, Wilcoxon signed-rank test and McNemar's test. The level of significance was set at 2-tailed $P < 0.05$ for all tests. All analysis were performed with the SAS statistical package (version 9.4; SAS Institute, Cary, NC).

3. Results

3.1. Baseline demographic and clinical data

Characteristics of the patients included in the evaluable population are shown in Table 1. The lowest mean duration of asthma corresponded to the severe eosinophilic asthma (early and late onset) with 15.6 (SD, ± 9.4) years and the highest to early onset allergic asthma with 24.2 (SD, ± 13.5) years (Table 2). The mean duration of persistent severe asthma at baseline was 7.0 (SD, ± 5.2) years for the whole study population, corresponding the lowest time elapsed, 6.3 (SD, ± 3.8) years, to severe asthma with frequent exacerbations and the highest, 7.8 (SD, ± 7.3) years, to early onset allergic asthma (Table 2).

3.2. Distribution of asthma phenotypes

The distribution of patients in the asthma phenotypes was as follows: severe asthma with frequent exacerbations (103 patients, 29.9%), early-onset allergic asthma (82 patients, 23.8%), severe steroid-dependent asthma (62 patients, 18.8%), severe eosinophilic asthma (47 patients, 13.6%), asthma with fixed air-flow obstruction (32 patients, 9.3%), and severe asthma in obese women (19 patients, 5.5%).

Table 1

Demographics and clinical characteristics at baseline.

Demographic or Clinical Characteristic	n = 345
Sex, n (%)	
Female	230 (66.7)
Age (years), mean (SD)	48.6 (15.4)
BMI (kg/m ²), Mean (SD)	27.4 (5.6)
Smoking status, n (%)	
Never	274 (79.4)
Former (≥ 1 year)	56 (16.2)
Current	15 (4.4)
Duration of asthma (years)	
Mean (SD)	19.4 (12.7)
Median (Q1, Q3)	15.9 (9.1, 26.1)
Duration of severe asthma until therapy with omalizumab (years)	
Mean (SD)	7.0 (5.2)
Median (Q1, Q3)	5.6 (4.2, 7.7)
Median FEV ₁ , % (Q1, Q3)	71.0 (60.0, 83.0)
IgE (IU/mL), median (Q1, Q3)	287.0 (132.0, 575.0)
Positive skin prick test to environmental allergens, n (%)	265 (76.8)
Blood eosinophils (%), median (Q1, Q3) ^a	5.0 (3.0, 8.0)
FeNO (ppb), median (Q1, Q3) ^b	35.0 (21.0, 51.0)
Family history of atopy, n (%)	122 (35.4)
Comorbidities, n (%)	
Allergic rhinitis	223 (64.6)
Sinus polyposis	81 (23.5)
Chronic sinusitis	44 (12.8)
Atopic dermatitis	32 (9.3)

^a Blood eosinophils value was available in 293 (84.9%) patients.

^b FeNO value was available in 146 (42.3%) patients.

3.3. Asthma symptoms, use of corticosteroids and rescue therapy, and control of asthma

During the previous year to therapy with omalizumab, 29.0% of the patients had symptoms more than 2 days a week, 50.1% presented daily symptoms, and 18.0% referred diurnal and nocturnal symptoms (only a few of them referred symptoms less than 2 days a week). After one year of treatment with omalizumab, 55.4% of the patients were asymptomatic, whereas the remaining patients (44.6%) had symptoms just one day (35.4%) or 2 days per week (9.3%).

After one year of treatment with omalizumab the number of patients receiving therapy with inhaled corticosteroids, leukotriene receptor antagonists, long-acting β_2 -agonists, short-acting β_2 -agonists, and theophylline had decreased in all phenotypes (Table 3).

In the case of oral corticosteroids, 207 patients (60.0%) required oral corticosteroids during the previous year to omalizumab therapy, 183 of them as maintenance therapy, with a median of 4.0 (2.0, 5.0) oral corticosteroids courses. After the first year of treatment with omalizumab, 33 (9.6%) continued taking oral corticosteroids as maintenance therapy ($P < .0001$). Oral corticosteroids requirements by phenotype are shown in Fig. 1.

Regarding the ACT results at both baseline and after one year of treatment with omalizumab were available for 129 (37.4%) of the patients. The mean ACT scores changes were as follows: +7.7 (SD, ± 3.2 ; 95% CI: 6.7, 8.7) in asthma with frequent exacerbations, +7.3 (SD, ± 4.2 ; 95% CI: 5.7, 8.9) in early-onset allergic asthma, +6.8 (SD, ± 3.7 ; 95% CI: 5.0, 8.5) in severe steroid-dependent asthma, +9.8 (SD, ± 4.2 ; 95% CI: 7.7, 11.9) in severe eosinophilic asthma, +8.4 (SD, ± 3.9 ; 95% CI: 6.4, 10.4) in asthma with fixed air-flow obstruction, and +7.0 (SD, ± 3.7 ; 95% CI: 2.4, 11.6) in severe asthma in obese women.

3.4. Pulmonary function

There was a significant improvement of FEV₁ after the first year of treatment with omalizumab in all phenotypes. The median FEV₁% increase was 13.0 (14.0, 20.0) in the global population ($P < .0001$), 14.0 (4.0, 27.0) in asthma with frequent exacerbations ($P < .0001$), 11.5 (1.0, 22.0) in early-onset allergic asthma ($P < .0001$), 13.0 (6.0, 23.0) in

Table 2
Asthma phenotypes characteristics (Baseline).

Characteristic	Early-onset allergic asthma n = 82	Severe asthma with frequent exacerbations n = 103	Asthma with fixed air-flow obstruction n = 32	Severe steroid-dependent asthma n = 62	Severe eosinophilic asthma n = 47	Severe asthma in obese women n = 19
Duration of asthma (years)						
Mean (SD)	24.2 (13.5)	18.6 (13.1)	18.6 (13.4)	18.8 (11.6)	15.6 (9.4)	16.1 (10.6)
Median (Q1, Q3)	22.8 (14.7, 33.9)	14.4 (8.4, 25.5)	12.1 (8.1, 27.8)	17.3 (10.3, 24.7)	12.9 (8.9, 19.6)	12.0 (8.6, 19.7)
Duration of severe asthma until therapy with omalizumab (years)						
Mean (SD)	7.8 (7.3)	6.3 (3.8)	6.7 (4.2)	7.7 (5.0)	6.7 (4.7)	6.8 (3.6)
Median (Q1, Q3)	5.9 (4.2, 7.5)	5.4 (3.8, 7.2)	5.7 (4.3, 8.0)	6.3 (4.5, 8.8)	5.3 (4.3, 7.2)	5.8 (4.4, 9.2)
Median FEV ₁ , % (Q1, Q3)	74.0 (62.0, 87.0)	70.5 (60.0, 82.0)	61.0 (52.5, 67.0)	72.0 (58.0, 80.0)	76.0 (65.0, 90.0)	72.0 (67.0, 77.0)
IgE (IU/mL), median (Q1, Q3)	427.0 (208.0, 774.0)	227.0 (113.5, 474.0)	308.5 (178.0, 678.0)	182.0 (100.0, 526.0)	362.0 (181.0, 646.0)	191.0 (72.0, 288.0)
Positive skin prick test to environmental allergens, n (%)	81 (98.8)	74 (71.8)	24 (75.0)	40 (64.5)	35 (74.5)	11 (57.9)
Blood eosinophils (%), median (Q1, Q3)	6.0 (4.0, 8.0)	6.0 (3.0, 8.0)	5.0 (2.0, 8.0)	4.0 (2.0, 7.0)	8.0 (5.0, 10.0)	3.0 (2.0, 7.0)
FeNO (ppb), median (Q1, Q3)	45.5 (23.0, 60.0)	35.0 (22.0, 49.0)	24.0 (14.0, 34.0)	33.5 (22.0, 45.0)	48.0 (21.0, 62.0)	27.0 (25.0, 50.0)

Table 3
Asthma therapy at baseline and after one year of treatment with omalizumab.

Variable	Baseline n = 345	After omalizumab treatment n = 345	P value
Asthma therapy, n (%)			
Inhaled corticosteroids	344 (99.7)	313 (90.7)	<.0001 ^a
Oral corticosteroids	207 (60.0)	34 (9.9)	<.0001 ^a
Long-acting beta2-agonist	336 (97.4)	294 (85.2)	<.0001 ^b
Short-acting beta2-agonist	328 (95.1)	227 (65.8)	<.0001 ^b
Leukotriene receptor antagonists	296 (85.8)	207 (60.6)	<.0001 ^b
Theophylline	35 (10.1)	8 (2.3)	<.0001 ^b
Tiotropium bromide	23 (6.7)	16 (4.6)	>.05 ^b
Ipratropium bromide	15 (4.4)	8 (2.3)	>.05 ^b

^a P-value with McNemar test.

^b Fisher's exact (Two-tailed).

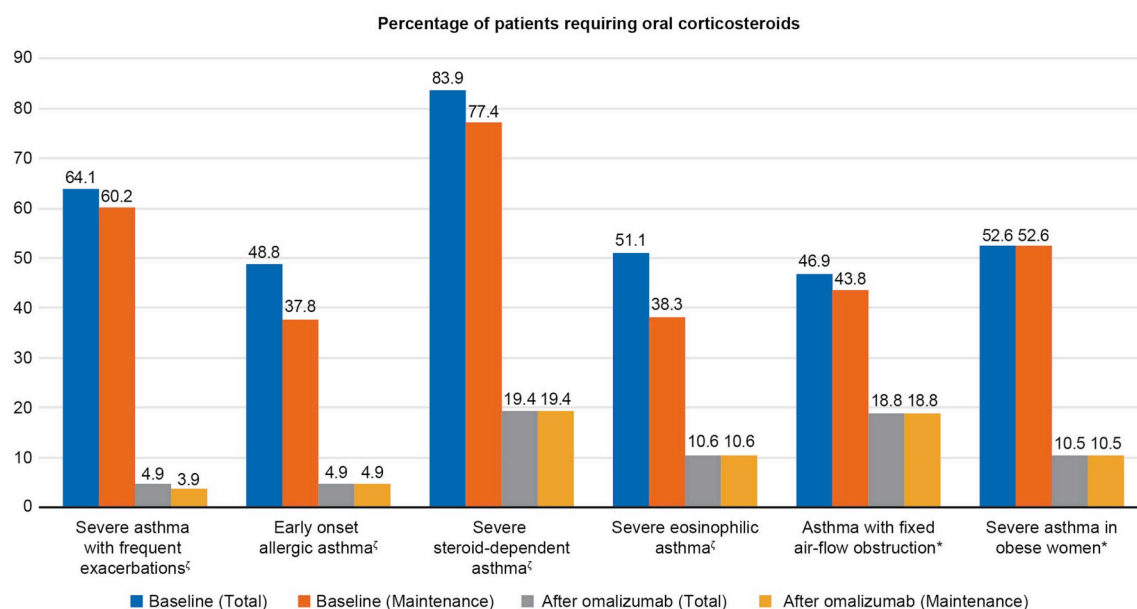
severe steroid-dependent asthma ($P < .0001$), 15.5 (5.5, 24.0) in severe eosinophilic asthma ($P < .0001$), 11.0 (2.0, 23.5) in fixed air-flow obstruction asthma ($P < .0001$), and 15.0 (7.0, 24.0) in severe asthma in obese women ($P = .0002$). FEV₁% median values per phenotype, at baseline and after the first year of treatment with omalizumab, are shown in Fig. 2.

3.5. Asthma exacerbations

In the full population of patients, the median of non-severe asthma exacerbations was 5.0 (3.0, 8.0) at baseline. It significantly reduced to 1.0 (0.0, 2.0) ($P < .0001$) during the first year of treatment with omalizumab. Significant results were found in all asthma phenotypes (Fig. 3).

3.6. Scholar and workplace absenteeism

A significant change ($P < .0001$) of the number of days with scholar or workplace absenteeism was observed after the treatment with omalizumab, with a median change of 0.0 (−13.0, 0.0) days ($P < .0001$).



^c $P < 0.0001$; ^{*} $P < 0.1$

Fig. 1. Oral corticosteroids at baseline and after one year of treatment with omalizumab.

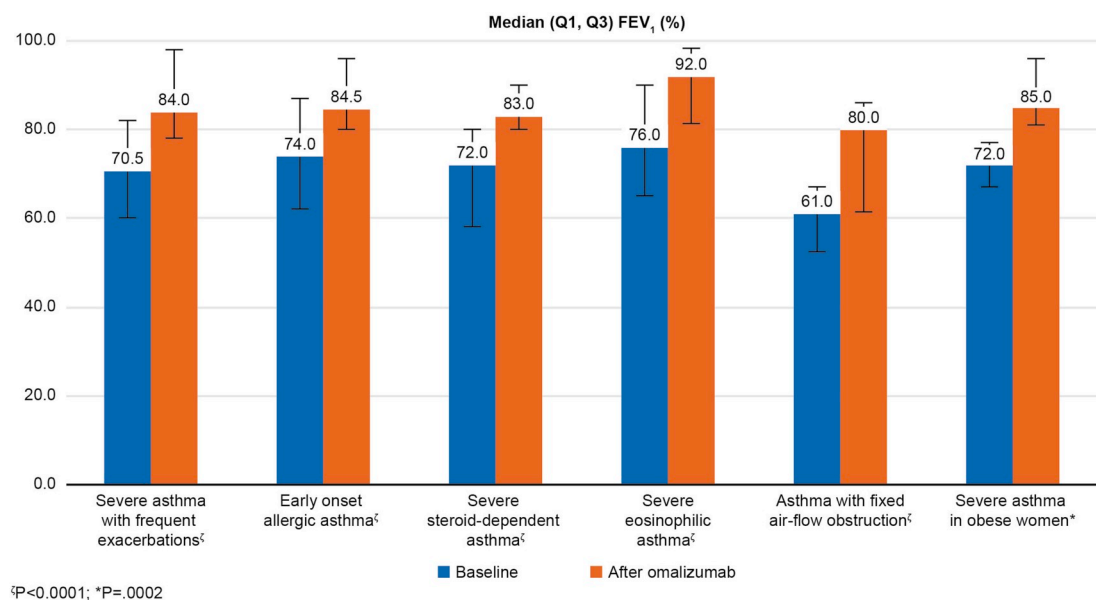


Fig. 2. FEV₁ at baseline and after one year of treatment with omalizumab.

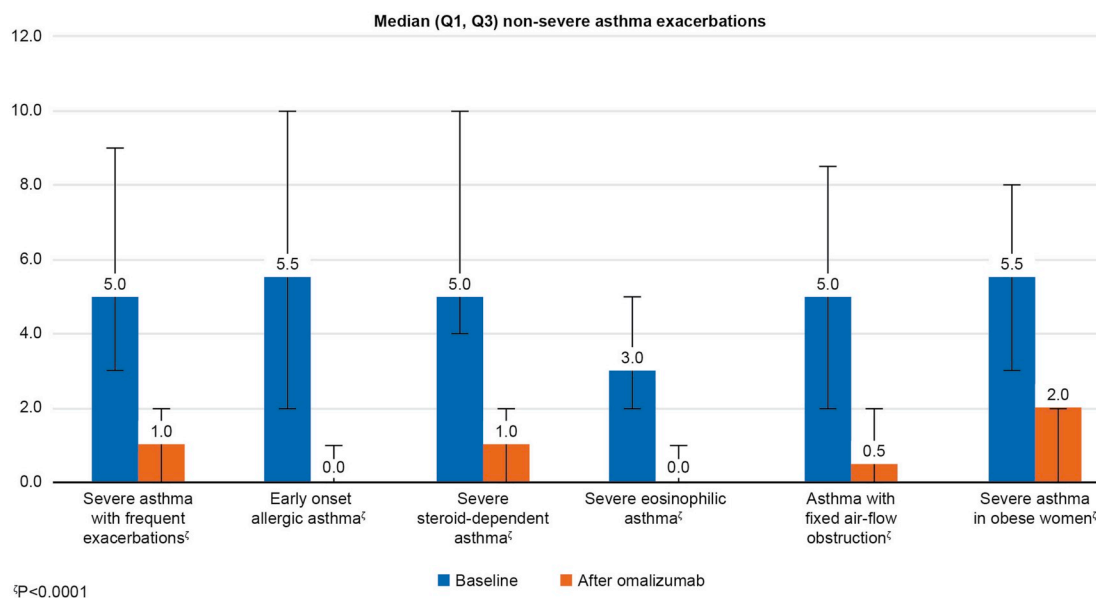


Fig. 3. Non-severe asthma exacerbations at baseline and after one year of treatment with omalizumab.

This change was statistically significant in all asthma phenotypes ($P \leq .002$), except that of obese women with severe asthma ($P = .1250$).

3.7. Biological markers

The median baseline values of blood eosinophils and FeNO in the whole population were, respectively, 5.0% (3.0, 8.0) and 35.0 ppb (21.0,

51.0). Values per phenotype are shown at Table 2. In those patients with available data at both baseline and after the first year of treatment with omalizumab, blood eosinophils count and FeNO decreased in all phenotypes, except peripheral eosinophils in obese women with severe asthma. Data shown in Table 4.

Table 4
Biological markers change after one year of treatment with omalizumab.

Characteristic	Early-onset allergic asthma	Severe asthma with frequent exacerbations	Asthma with fixed air-flow obstruction	Severe steroid-dependent asthma	Severe eosinophilic asthma	Severe asthma in obese women
Blood eosinophils (%), median (Q1, Q3) change	−2.0 (−5.0, −1.0)	−1.0 (−4.0, 0.0)	−2.0 (−4.0, 0.0)	−1.0 (−3.0, 0.0)	−2.0 (−6.0, −1.0)	0.0 (−2.0, 1.0)
FeNO (ppb), median (Q1, Q3) change	−16.5 (−29.5, 0.0)	−7.0 (−24.0, 0.0)	−7.0 (−20.0, +1.0)	−14.0 (−26.0, −2.0)	−10.0 (−21.0, +9.0)	−17.0 (−40.0, −3.0)

4. Discussion

To our knowledge, this is the first real-life study addressing the response of different asthma phenotypes in severe asthma patients showing good response to omalizumab. Thus, therapy with omalizumab was associated with an improvement of asthma symptoms, a decrease in the use of oral and inhaled corticosteroids, with fewer non-severe asthma exacerbations, and a better pulmonary function. These findings were noted in all asthma phenotypes, even in those patients diagnosed by their physicians with steroid-dependent or fixed airflow obstruction asthma. This improvement was achieved in all clinical phenotypes regardless of the duration of asthma.

Numerous real-world studies have shown the effectiveness of omalizumab in terms of improvement of asthma symptoms and lung function; reduction of asthma exacerbations and hospitalizations, and in the use of inhaled and oral corticosteroids [24–27,33,34].

This study provides data on a population of patients with complete asthma control, according to GEMA [29], after the first year of therapy with omalizumab. In this study population, the most frequent phenotype was severe asthma with frequent exacerbations (29.9%), followed by early-onset allergic asthma (23.8%), severe steroid-dependent asthma (18.8%) and severe eosinophilic asthma (13.6%). The distribution of the phenotypes found in this study highlights the heterogeneity of asthma and its clinical manifestations, and the effectiveness of omalizumab in various asthma phenotypes. Although other factors such as prevalence differences, and physician treatment selection bias cannot be ruled out to explain the phenotype distribution, a better definition of patient profiles is needed to correlate phenotypes and endotypes with the underlying inflammation. In this regard, clustering analysis could be valuable.

Although omalizumab has shown efficacy in patients with allergic asthma [25,27,35], its value in the treatment of other asthma phenotypes remains to be understood, including non-allergic asthma [36]. In this study, some patients who achieved good asthma control after one year of omalizumab therapy had negative skin prick tests and no allergic sensitization was found. Similar observations indicating the potential benefit of omalizumab in non-atopic patients have been reported [37, 38].

Large studies of severe asthma in the last decade have expanded our understanding of the range of characteristics associated with severe asthma. To understand the different groups better, initial studies attempted to define phenotypes of severe asthma. Both clinical and statistical approaches identified at least 3–5 phenotypes of severe asthma [14,15,39].

Emerging data from large cohorts strongly support heterogeneity in severe asthma, with increasing acceptance of the presence of distinct phenotypes [7]. However, these phenotypes, in isolation, do not identify the immunopathology that make these clinical phenotypes distinct nor identify a target population for a specific approach to therapy. As biological characteristics are identified, phenotype definitions should evolve further. Regarding this issue, cluster analyses have also been applied to identify characteristics of severe asthma. An extensive analysis conducted in SARP, yielded three phenotypic clusters of patients with severe asthma identified by lower lung function, a requirement for more controller medications, and, despite high medication use, more frequent exacerbations [14]. However, these clusters were not uniformly distributed and patients not only differed in clinical characteristics but also biomarker profiles [40–44]. Thus, the predefinition of the phenotype groups, rather than using clustering analysis, could also be a limitation, as this is a quickly evolving field, and some patients could indeed be assigned to more than one of the predefined groups, as some of them have overlapping characteristics. It is important to note that the “state of the art” in this field and, consequently, the clinical practice, have experienced important changes since this study was designed, and will probably change further in the coming years.

Interestingly, in the current study, the treatment with omalizumab

based on total and allergen-specific IgE levels was not completely effective in identifying patients likely to respond to therapy. Approximately 23.2% of patients with an excellent response to omalizumab had negative skin tests. Therefore, biomarkers to identify patients who respond to treatment with omalizumab are required [45,46]. However, a reduction in high FeNO and peripheral eosinophils after treatment with omalizumab was also found in our previous findings [25,47]. In agreement with the overall improvement, patients had significantly fewer days of scholar or workplace absenteeism across all phenotypes except in obese women with severe asthma. These reductions with omalizumab were observed in previous studies in patients with severe asthma [23,24].

Although the impact of co-morbidities on patients’ suffering out of scope for this study, it is critical to note that they play a significant role in the management of severe asthma and may lead to poor control and over-treatment for anti-asthmatic conditions [48]. Indeed, the SARP study categorized obesity to be associated with severe late-onset asthma predominantly in females [14]. Obese patients suffering from severe asthma report lower lung function along with higher IL-5 and eosinophil levels [49]. The impact of treatment with omalizumab in obese women was difficult to assess in this study as the obese group of patients were underrepresented, therefore, complicating the assessment of findings of non-significant reduction in scholar or workplace absenteeism and no decline in the level of peripheral eosinophils.

The retrospective study design of this study helped to assess associations between drug exposure and outcomes especially with reference to the different phenotypes [50]. However, the main limitations of this study were the non-interventional and retrospective design, the absence of a control group, and the high overlap among phenotype categories, with possible patient and treatment selection biases. Being a retrospective study in which all data were recorded at baseline, an opportunity to have results from repeated measurements during the course with omalizumab was missing. A Post hoc analysis of the allergic and non-allergic patients included in this study, and studies with a clustering analysis methodology, would probably be helpful to obtain further knowledge to establish profiles of patients with good response to omalizumab.

5. Conclusions

In patients with persistent severe asthma who achieved a good control of the disease during the first year of treatment with omalizumab, the most frequent phenotypes found were severe asthma with frequent exacerbations, and early onset allergic asthma. Clinical phenotypes were characterized by high IgE, peripheral blood eosinophils and FeNO at baseline, suggesting that these factors could be, overall, determinants of response. Treatment with omalizumab was associated with an improvement in symptoms and pulmonary function, and reduction of peripheral blood eosinophilia and FeNO. Corticosteroids use and rescue therapy with β_2 -agonists were reduced. After one year of treatment with omalizumab, there were very few episodes of non-severe asthma exacerbations and less scholar or work absenteeism. Further studies in severe asthma patients are needed to understand the impact of phenotypes on the treatment guidelines and their influence on current clinical practices in asthma.

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Declaration of competing interest

Paloma Campo declares the following potential conflict(s) of interest to report: Bial, Novartis, Astra-Zeneca, GSK: advisory boards and speakers’ honoraria.

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