Respiratory Medicine 119 (2016) 141–149

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Effects of omalizumab in severe asthmatics across ages: A real life Italian experience

B. Sposato [a, *], M. Scalese [b], M. Latorre [c], N. Scichilone [d], A. Matucci [e], M. Milanese [f], S. Masieri [g], G. Rolla [h], G. Steinhilber [i], Y. Rosati [j], A. Vultaggio [e], I. Folletti [k], S. Baglioni [l], E. Bargagli [m], M. Di Tomassi [a], R. Pio [n], A. Pio [n], U. Maccari [o], C. Maggiorelli [o], M.G. Migliorini [a], L. Vignale [p], N. Pulerà [q], G.E. Carpagnano [r], M.P. Foschino Barbaro [r], A. Perrella [a], P.L. Paggiaro [c]

[a] Pneumologia, Ospedale Misericordia, Grosseto, Italy
[b] Istituto di Fisiologia Clinica, CNR, Pisa, Italy
[c] Cardio Thoracic and Vascular Department, Pathophysiology Unit, University of Pisa, Italy
[d] DIMPEFINU, Unit of Pneumology and Medicine, University of Palermo, Palermo, Italy
[e] Immunoallergology Unit, Department of Medicine and Geriatric, AOU Careggi, Florence, Italy
[f] Pneumologia, Ospedale S.Corona, Pietra Ligure, Italy
[g] Clinica Otorinolaringoiatrica, Policlinico Umberto I, Università di Roma "Sapienza", Italy
[h] Allergologia e Immunologia Clinica, Ospedale Mauriziano Umberto I, Università di Torino, Italy
[i] Pneumologia Spedali Civili di Brescia, Italy
[j] Pneumologia, Ospedale di Macerata, Italy
[k] Sezione di Medicina del Lavoro, Malattie Respiratorie e Tossicologia Professionale ed Ambientale, Dipartimento di Medicina, Università di Perugia, Az. Ospedaliera Santa Maria, Terni, Italy
[l] Pneumologia, AOU di Perugia, Italy
[m] Pneumologia, Ospedale Le Scotte, Università di Siena, Italy
[n] Allergologia e Immunologia Clinica, Ospedale G. Fucito, Mercato S. Severino, Salerno, Italy
[o] Pneumologia e UTIP, Ospedale "S.Donato", Arezzo, Italy
[p] Pneumologia, Ospedale di Fivizzano, Italy
[q] Pneumologia, Ospedale di Livorno, Italy
[r] Institute of Respiratory Disease, Department of Medical and Occupational Sciences, University of Foggia, Italy

ARTICLE INFO

Article history:
Received 19 May 2016
Received in revised form
31 August 2016
Accepted 2 September 2016
Available online 4 September 2016

Keywords:
Omalizumab
Severe asthma
Elderly
Real-life
Age effect

ABSTRACT

Background: This retrospective study aimed at evaluating long-term effects of Omalizumab in elderly asthmatics in a real-life setting.
Methods: 105 consecutive severe asthmatics (GINA step 4–5; mean FEV_1% predicted:66 ± 15.7) treated with Omalizumab for at least 1 year (treatment mean duration 35.1 ± 21.7 months) were divided into 3 groups according to their age at Omalizumab treatment onset: 18–39, 40–64 and ≥ 65 years.
Results: Comorbidities, number of overweight/obese subjects and patients with late-onset asthma were more frequent among older people. A similar reduction of inhaled corticosteroids dosage and SABA on-demand therapy was observed in all groups during Omalizumab treatment; a similar FEV_1 increased was also observed. Asthma Control Test (ACT) improved significantly ($p < 0.001$) in the three groups, increasing from 15 [IQR:12-18] to 24 [IQR:22-25] in younger subjects, from 14 [IQR:10-16] to 21 [IQR:20-23] in the 40-64-year-group and from 15 [IQR:12-16] to 20 [IQR:18-22] in elderly patients where improvement was lower ($p = 0.039$) compared to younger people. Asthma exacerbations decreased significantly after Omalizumab but the percentage of exacerbation-free patients was higher in younger people (76.9%) compared to middle aged patients (49.2%) and the elderly (29%) ($p = 0.049$).
After Omalizumab treatment, the risk for exacerbations was lower in subjects aged 40–64 (OR = 0.284 [CI95% = 0.098–0.826], $p = 0.021$) and 18–39 (OR = 0.133 [CI95% = 0.026–0.678], $p = 0.015$), compared to elderly asthmatics. Also, a significantly reduced ACT improvement ($\beta = -1.070$; $p = 0.046$) passing from each age class was observed.

* Corresponding author. U.O. Pneumologia, Azienda Ospedaliera "Misericordia", Via Senese 161, 58100 Grosseto, Italy.
E-mail address: bsposat@tin.it (B. Sposato).

http://dx.doi.org/10.1016/j.rmed.2016.09.005

Conclusion: Omalizumab improves all asthma outcomes independently of age, although the magnitude of the effects observed in the elderly seems to be lower than in the other age groups.

1. Introduction

Severe asthma is defined as the requirement for high-intensity treatment to obtain disease control [1]. However, despite the use of high doses of inhaled corticosteroids (ICS), long acting bronchodilators and anti-leukotrienes, optimal asthma control is not achieved in the vast majority of patients. In this case, the adding of Omalizumab, a recombinant DNA-derived humanized monoclonal antibody, is recommended according to GINA guidelines step 4 or 5 (severe persistent uncontrolled asthma allergic to perennial allergens) [2]. Omalizumab has been demonstrated to be efficacious both in adults and children [3–5]. In particular, in real-life studies, anti-IgE therapy showed short and long-term benefits with regard to lung function and quality of life improvement, the achievement of asthma control and the reduction of exacerbations, healthcare resource utilizations, hospitalizations, emergency department visits and asthma medications thus confirming, complementing and extending evidence from randomized clinical trials [3,5].

However, studies designed to test the effectiveness of Omalizumab do not include elderly subjects. Therefore, it is not known whether Omalizumab treatment is also effective in elderly severe asthmatics. To the best of our knowledge, only one real life study tried to evaluate this by observing similar clinical outcome improvements in asthmatics under and over 50 years of age, without specifically confirming a possible positive effect in patients aged >65 years. Furthermore, treatment in this study only lasted for a short period (4 months only), thus not showing how effective Omalizumab is above all in the elderly [6]. In this category of subjects, asthma may differ from asthma in younger individuals [7]. The pathophysiological mechanisms of such disease may be affected by structural and functional changes of senile lungs, which may influence asthma clinical course as well as its response to treatment in older individuals [8]. In fact, elderly asthmatic subjects report lower post-bronchodilator FEV_1%, more exacerbations and an increased risk of a first severe exacerbation (by 55.3%) when compared to younger patients [8]. A body of literature suggests that asthma in the elderly might represent a specific phenotype characterized by a more severe, but often less perceived, airway obstruction, a neutrophilic or mixed-type of airway inflammation and frequent comorbidities [7,9,10]. Older asthmatics are often characterized by long-standing asthma that has a more severe airflow limitation and less complete reversibility (or even irreversibility) than in late-onset asthma patients [11]. In subjects with advanced age, asthma may also be complicated by an airways neutrophilic inflammation that may be associated to a more severe obstructive disease and a poor response to treatment [9–13]. In fact, asthma in the elderly may be worsened by COPD involving about 28% of asthmatics aged >65 years (14,15). As already said, asthma-COPD overlap may influence severity and disease control (14,15) and probably also the treatment effect. In addition, elderly asthmatics usually have multiple chronic comorbid conditions that can be also associated with poor asthma outcomes [14–16]. For this reasons, severe asthma in the elderly may be a more complex and complicated disease than in younger individuals.

The aim of this study was to assess whether in a real-life setting long-term Omalizumab treatment is effective in elderly severe uncontrolled asthmatics.

2. Materials and methods

Eighteen Italian secondary care centers were involved in this retrospective study. To be part of this observational study, each center was asked to provide data of at least 3 consecutive severe allergic asthmatics (step 4–5 according to GINA criteria) [2] under treatment with Omalizumab, for at least 1 year. All subjects showed a previous asthma diagnosis based on GINA recommendations [2] allergic to perennial allergens and had to show a poor disease control with high doses of ICS plus LABA and montelukast. For this reason Omalizumab had been prescribed too. Demographic, clinical and functional data were extracted from patients' clinical records and registered in a previously agreed form. Information concerning allergic sensitization *(Dermatofagoides pteronissinus* and *D. farinae*, Grass mix, *Parietaria*, *Olea europaea*, *Cupressus sempervirens*, *Betula pendula*, *Alternaria tenuis, Aspergillus f.* and dog-cat dander), serum IgE values, the presence of rhinitis, sinusitis, nasal polyposis, and/or other comorbidities (systemic hypertension, chronic heart disease, diabetes, osteoporosis, gastro-esophageal reflux, COPD, obesity), smoking habits and body mass index (BMI), observed at the beginning of Omalizumab treatment, were required for each patient. Furthermore, age of asthma onset, Omalizumab dosing and period of treatment were recorded. For the purpose of the study, lung function variables (FEV_1, FVC, FEV_1/FVC), Asthma Control Test (ACT), medications used, number of moderate/severe exacerbations, ICS doses and use of rescue medication were evaluated and compared. Data were collected between November 2014 and November 2015. A total of 105 severe asthmatics were recruited. The study protocol was approved by the Ethic Commitee of Pisa University Hospital. Informed consent was obtained from all participants.

To the aims of the study, recruited patients were arbitrarily divided into 3 groups on the basis of the age observed at the onset of Omalizumab treatment: 18–39 yrs, 40–64 yrs and ≥65 yrs. This distinction allowed to better differentiate the effectiveness of treatment in the elderly as opposed to younger individuals.

Moderate/severe exacerbations that required systemic corticosteroids for at least 3 days and/or hospitalizations were taken into account. Obesity was defined by a BMI >30. The use of ICS with daily dosage was expressed as low (≤500 μg), medium (500–1000 μg) or high (≥1000 μg) dosage of beclomethasone dipropionate, CFC or equivalent according to GINA classification [2]. The latest FEV_1, ACT score, the number of exacerbations and daily dosage of ICS reported the year before taking Omalizumab and at the end of the last year of treatment with anti-IgE (before subjects were recruited for the study) were considered. The use of SABA (number of times a week) in the month before starting Omalizumab and before the beginning of this study was also taken into account. As regards comorbidities, only those which had documented evidence were considered. Diagnosis of COPD as concomitant disease was established when subjects showed chronic cough/phlegm and smoking history associated to hyperinflation shown by spirometry (TLC>120% of predicted) and/or single breath CO diffusion test (DLCO) < 80% of predicted and/or central-panlobular emphysema seen by high resolution computed tomography (HRCT).

2.1. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile [IQR] range. Categorical variables were expressed as number of cases and percentages.

Comparisons of continuous variables among the age groups were performed by using the Kruskal–Wallis test. The Wilcoxon signed-rank test was used to assess the difference between "before" and "after" treatment. The categorical variable frequencies were compared by chi-square test or Fisher's exact test, as appropriate. Post-hoc prevalence comparisons were made by the X^2 test with Bonferroni correction; this analysis was also used as a post-hoc test to compare non-parametric data. A logistic binary regression model (stepwise forward procedure), was applied to evaluate whether age, sex, BMI, FEV_1, sensitizations, IgE value, comorbidities, smoking, age of asthma onset, Omalizumab treatment duration, daily doses of ICS and montelukast use, were independent risk factors for exacerbations (vs zero exacerbations) after Omalizumab treatment. Furthermore, a linear regression model (stepwise forward procedure), was also performed with the purpose to evaluate whether all the above reported parameters (considering three classes of age: 18–39, 40–64 and ≥ 65 years) were independently related to ACT changes obtained after Omalizumab treatment. Comorbidities like allergic rhinitis, rhinosinusitis, nasal polyps, gastro-oesophageal reflux disease, hypertension, chronic heart disease, diabetes, osteoporosis and COPD were examined individually in the models. Age was also considered as a continuous variable in the models. Both the logistic and regression models were also performed without considering the group of asthmatics affected by concomitant COPD (14 patients).

All calculations were done by using SPSS software. A $p < 0.05$ was considered as significant.

3. Results

Younger asthmatics (aged between 18 and 39 years) were 13 (12.4% of all patients; mean FEV_1: 67.2 ± 12.4% predicted), whereas patients aged between 40 and 64 years were 61 (58.1% of the entire study group; mean FEV_1: 65.6 ± 16% predicted) and those aged ≥65 years were 31 (29.5% of all patients; mean FEV_1: 66.2 ± 16.7%). Table 1 shows data from the three age groups. BMI was significantly lower ($p = 0.049$) in younger subjects. No differences in number of allergen sensitizations or serum total IgE values (evaluated before the Omalizumab therapy) were found in the three groups. Furthermore, no differences were observed in doses and time (months) of anti-IgE drug treatment. Also, the proportion of subjects in treatment with ICS, long-acting bronchodilators and montelukast (used before adding Omalizumab) was similar in the three groups. On the contrary, a higher number of comorbidities was registered in the older group.

Fig. 1 shows median FEV_1% predicted values measured before (pre) and after (post) Omalizumab. FEV_1% predicted before treatment (70% [IQR:60–76.6]; 68% [IQR:55-75]; 67% [IQR:58-79]; $p = 0.838$; Fig. 1/A) and after it (82.1% [IQR:73-88]; 82% [IQR:66-

Table 1
Comparisons of all variables, measured before treatment with Omalizumab, among the three different age groups.

	13 asthmatics aged 18–39 years	61 asthmatics aged 40–64 years	31 asthmatics aged ≥65 years	p
Age	29 ± 6*	54 ± 7*°	69 ± 4*°	0.0001
M/F	9/4*	16/45*	8/23*	0.007
Smokers	2 (15.4)	4 (6.6)	2 (6.5)	0.526
Ex Smokers	2 (15.4)	17 (27.9)	5 (16.1)	
Pack/year	4 ± 1	12 ± 8	13 ± 8	0.143
House dust mite	10 (76.9)	55 (90.2)	27 (87.1)	0.418
Pollens	12 (92.3)	41 (67.2)	18 (58.1)	0.086
Moulds	1 (7.7)	6 (9.8)	2 (6.5)	0.854
Cat/dog dander	4 (30.8)	22 (36.1)	10 (32.3)	0.899
Monosensitized (to 1 allergen)	2 (15.4)	18 (29.5)	12 (38.7)	0.299
Polisensitized (≥2 allergens)	11 (84.6)	43 (70.5)	19 (61.3)	
FEV_1%	67.2 ± 12.4	65.6 ± 16	66.2 ± 16.7	0.838
FEV_1/FVC	61.2 ± 10.5	58.4 ± 11.2	60.8 ± 11	0.642
Total IgE	379.9 ± 278.1	333 ± 260.1	342.3 ± 228.6	0.833
N° of subjects with rhinitis/sinusitis (%)	11 (84,6)	49 (80.3)	21 (67.7)	0.314
N° of subjects with nasal polyposis (%)	1 (7.7)	13 (21.3)	3 (9.7)	0.242
N° of subjects with Hypertension (%)	0	16 (26.2)	12 (38.7)	0.03
N° of subjects with Chronic Heart Disease (%)	0	6 (9.8)	3 (9.7)	0.499
N° of subjects with Diabetes (%)	0	5 (8.2)	2 (6.5)	0.560
N° of subjects with Osteoporosis (%)	0	10 (16.4)	9 (29)	0.064
N° of subjects with Gastro-esophageal reflux (%)	3 (23.1)	21 (34.4)	14 (45.2)	0.345
N° of subjects with COPD (%)	0	11 (18)	3 (9.7)	0.172
BMI	24.25 ± 2.65*	27.45 ± 5.17*	27.70 ± 3.41*	0.049
N° of subjects with Normal weight (%)	7 (53.8)	20 (33.3)	5 (16.1)	
N° of subjects with Overweight (%)	6 (46.2)	24 (40)	20 (64.5)	0.029
N° of subjects with Obesity (%)	0	16 (26.7)	6(19.4)	
N° of subjects with 0 comorbidity (%)	10 (76.9)	19 (31.1)	5 (16.1)	
N° of subjects with 1 comorbidity (%)	3 (23.1)	22 (36.1)	11 (35.5)	0.002
N° of subjects with ≥2 comorbidities (%)	0	20 (32.8)	15 (48.4)	
Age of asthma onset	14 ± 10*	34 ± 13*°	43 ± 17*°	0.0001
Omalizumab dosage	479 ± 276	420 ± 210	457 ± 233	0.602
Months of Omalizumab treatment	30 ± 22	36 ± 22	37 ± 22	0.610
Patients in treatment with ICS	13 (100)	61 (100)	31 (100)	1
Patients in treatment with LABA	12 (92.3)	58 (95.1)	29 (93.5)	0.906
Patients in treatment with Montelukast	10 (76.9)	46 (75.4)	21 (67.7)	0.699
Patients in treatment with Tiotropium	2 (15.4)	16 (26.2)	5 (16.1)	0.451

Post-hoc analysis was made by using Bonferroni test: *°statistically significant differences between groups when they were compared. Percentages of normal weight, overweight and obese patients were different between 18 and 39 years and >65 years groups (Bonferroni test; $p = 0.04$). Percentages of subjects with different number of comorbidities were different among all 3 groups (Bonferroni test; $p = 0.01$).

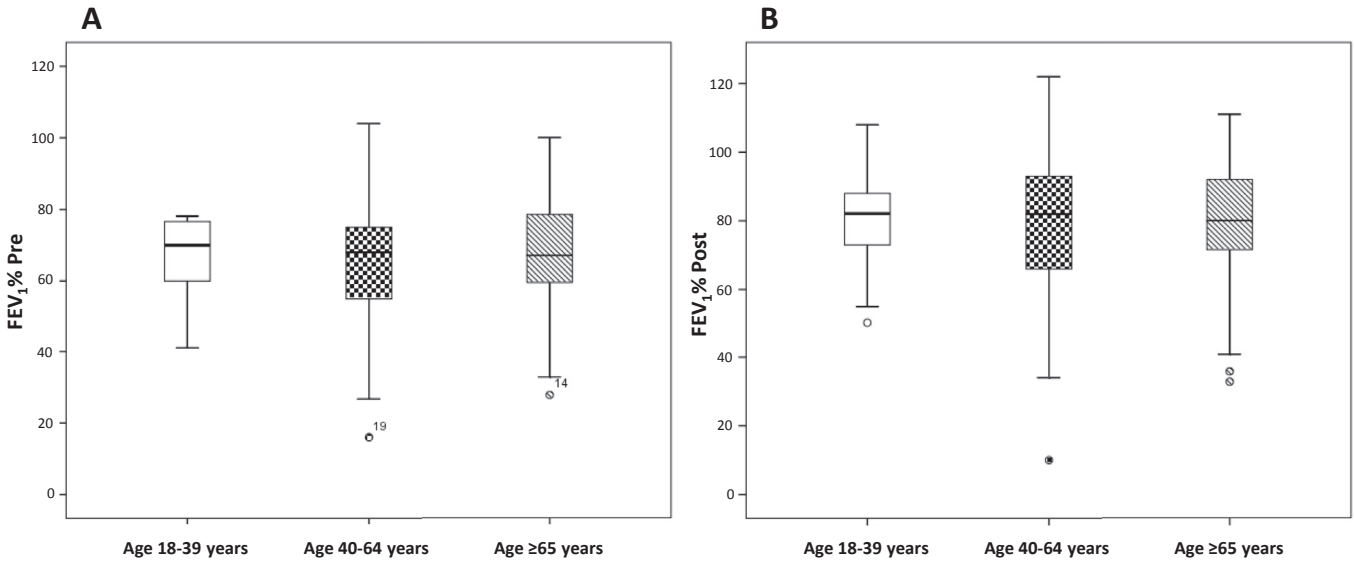

Fig. 1. FEV_1 values measured before (Pre) and after (Post) Omalizumab treatment. Data were expressed as median and Interquartile range. Comparison (Kruskal–Wallis test) between Pre and Post Omalizumab treatment in subjects aged 18–39 years: p = 0.002; in subjects aged 40–64 years: p = 0.0001; in subjects aged ≥65 years: p = 0.0001. Comparisons among subjects with different ages: pre-values p = 0.838; post-values: p = 0.906.

93]; 80% [IQR:71-92]; p = 0.906; Fig. 1/B), measured in younger, medium and older age groups (respectively) that did not differ among them. However, after Omalizumab treatment, FEV_1 improved significantly (p < 0.001; comparing pre-post) in each group. FEV_1 improvement was similar among three groups (Fig. 1/B). Also ACT values (Fig. 2) improved significantly (p < 0.001; comparing pre-post – Fig. 2 A and B) in each group (pre values: 15 [IQR:12-18]; 14 [IQR:10-16]; 15 [IQR:12-16]; post-values: 24 [IQR:22-25]; 21 [IQR:20-23]; 20 [IQR:18-22]; measured in young, middle-aged and elderly subjects respectively). However, the improvement in ACT appeared to be lower in asthmatics over 65 years (20 vs 15, post vs pre) when compared with younger subjects aged 18–39 years (24 vs 15, post vs pre); in fact, the post ACT value measured in younger subjects (24) was higher than the one observed in older patients (20) (p = 0.039; Fig. 2).

There was a significant reduction in the number of exacerbations after Omalizumab treatment in each group (Fig. 3; p < 0.0001). The number of exacerbations recorded before the anti-IgE treatment was similar in the three groups, but they dropped differently after Omalizumab treatment. In fact, 76.9% of younger subjects did not experience any exacerbations after Omalizumab treatment, as opposed to almost one out of two middle-aged patients (49.2%) and only one third of older asthmatics (29%) (p = 0.049). ICS doses decreased significantly and similarly after

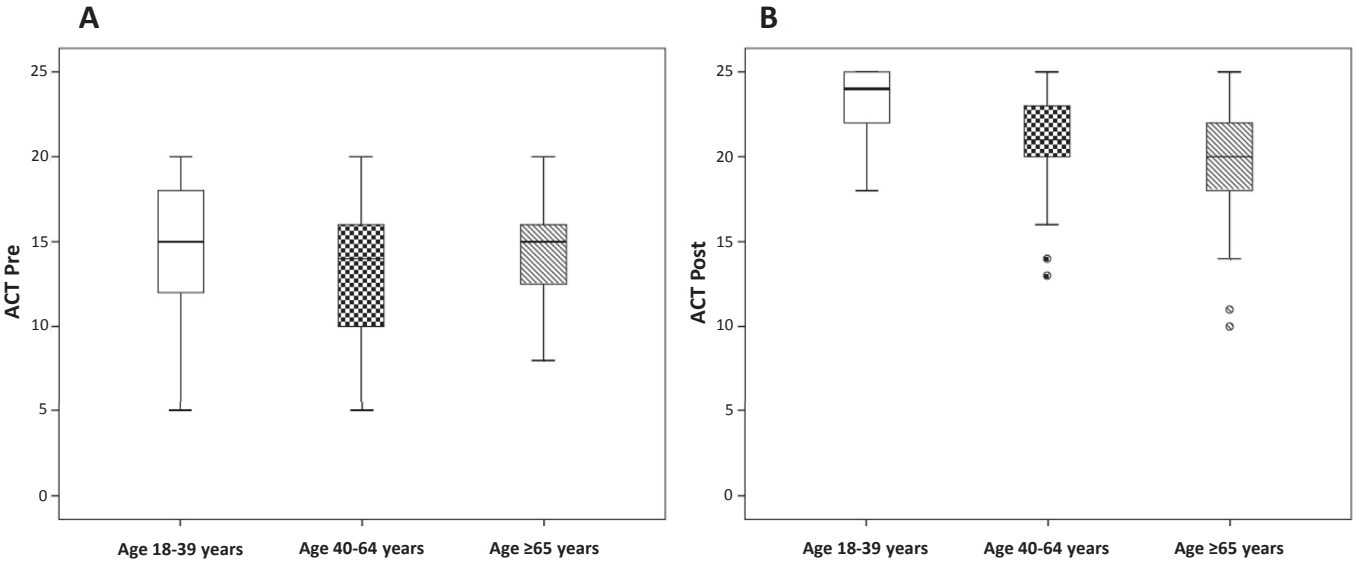

Fig. 2. Asthma Control Test (ACT) values (median plus IQR) measured before (Pre) and after (Post) Omalizumab treatment. Data were expressed as median and Interquartile range. Comparisons between Pre and Post Omalizumab treatment in subjects aged 18–39 years:p = 0.001; in subjects aged 40–64 years: p = 0.0001; in subjects aged ≥65 years: p = 0.0001. Comparisons among subjects with different ages: pre-values p = 0.383 (figure A); **post-values p = 0.039** (Figure B). Post-hoc analysis with Bonferroni test showed a statistical difference between values measured after Omalizumab treatment in the younger (18–39 years) and older groups: (>65 years) **p = 0.001** (Figure B).

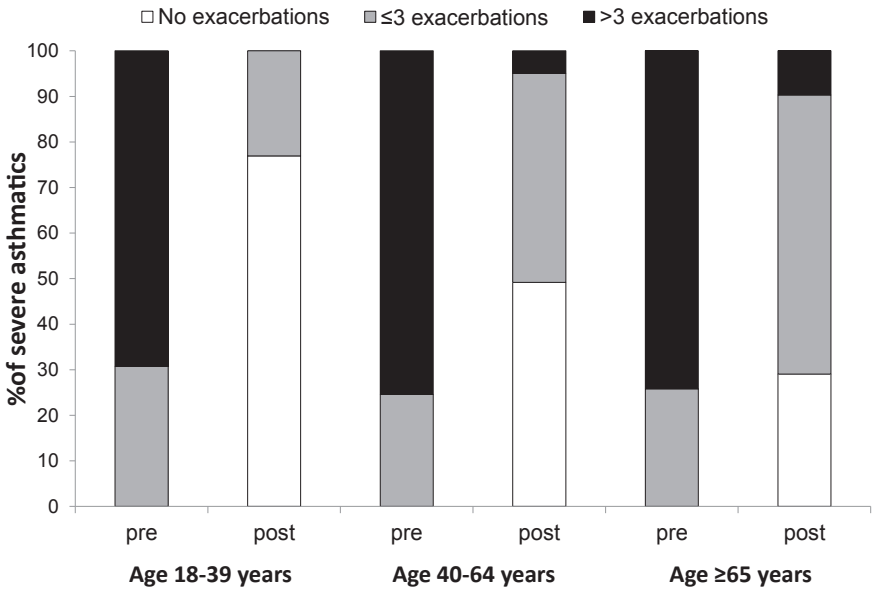

Fig. 3. Prevalence of subjects with different numbers of exacerbations observed in the year before (pre) and in the last year (post) of Omalizumab treatment in the 3 different age groups. Comparisons (Wilcoxon test) of prevalence observed before and after treatment with Omalizumab: $p = 0.021$ between pre-and post-treatment in subjects aged 18–39 years; $p = 0.001$ between pre-and post-treatment in subjects aged 40–64 years; $p = 0.0001$ between pre-and post-treatment in subjects aged ≥65 years. Comparisons (χ^2 test) of prevalence observed in subjects with different ages, before ($p = 0.898$) and after ($p = 0.049$) treatment with Omalizumab. A post hoc analysis (Bonferroni test) showed a prevalence difference between subjects aged 18–39 years and those aged ≥65 years ($p < 0.05$).

treatment in each group ($p < 0.01$; Fig. 4). We also observed a significant and similar reduction of SABA used as a rescue medication in all groups (Fig. 5).

Omalizumab demonstrated to be efficacious also in the 14 patients affected by asthma worsened by concomitant COPD when they were considered separately. In particular, FEV_1 increased from 57.7% to 70% ($p < 0.0001$), whereas ACT improved from 11 to 19 ($p < 0.0001$). Furthermore, 35% of them did not show any exacerbations during the last year of Omalizumab treatment. The improvement of ACT and the number of subjects with zero exacerbations after Omalizumab treatment were lower when compared to the younger group of severe asthmatics ($p < 0.05$) (data not shown either in tables or figures).

When a logistic model was applied, younger subjects showed a significantly lower risk for exacerbations (at least one) after Omalizumab treatment (subjects aged 40–64: OR = 0.284 [CI95% = 0.098–0.826], $p = 0.021$; subjects aged 18–39: OR = 0.133 [CI95% = 0.026–0.678], $p = 0.015$) in comparison to subjects over

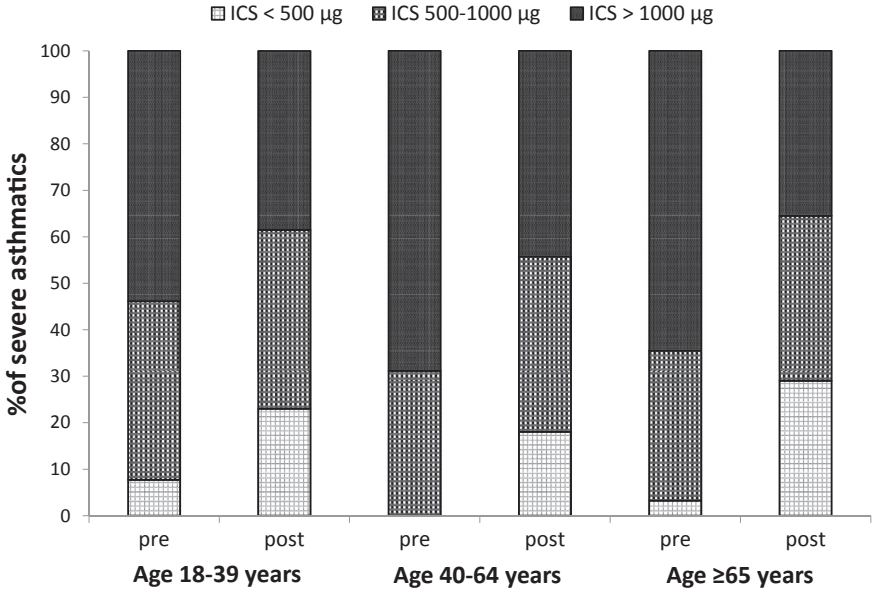

Fig. 4. Prevalence of subjects treated with different ICS levels used before (pre) and after (post) at least 1 year of Omalizumab in the 3 different age groups. Low doses of ICS: <500 µg equivalent to bechlometasone; Medium doses of ICS: 500–1000 µg equivalent to bechlometasone; High doses of ICS: >1000 µg equivalent to bechlometasone. Comparisons (test di Wilcoxon) of prevalence observed before and after treatment with Omalizumab: $p = 0.057$ between pre-and post-treatment in subjects aged 18–39 years; $p = 0.0001$ between pre-and post-treatment in subjects aged 40–64 years; $p = 0.001$ between pre-and post-treatment in subjects aged ≥65 years. Comparisons (χ^2 test) of prevalence observed in subjects with different ages, before ($p = 0.369$) and after ($p = 0.757$) treatment with Omalizumab.

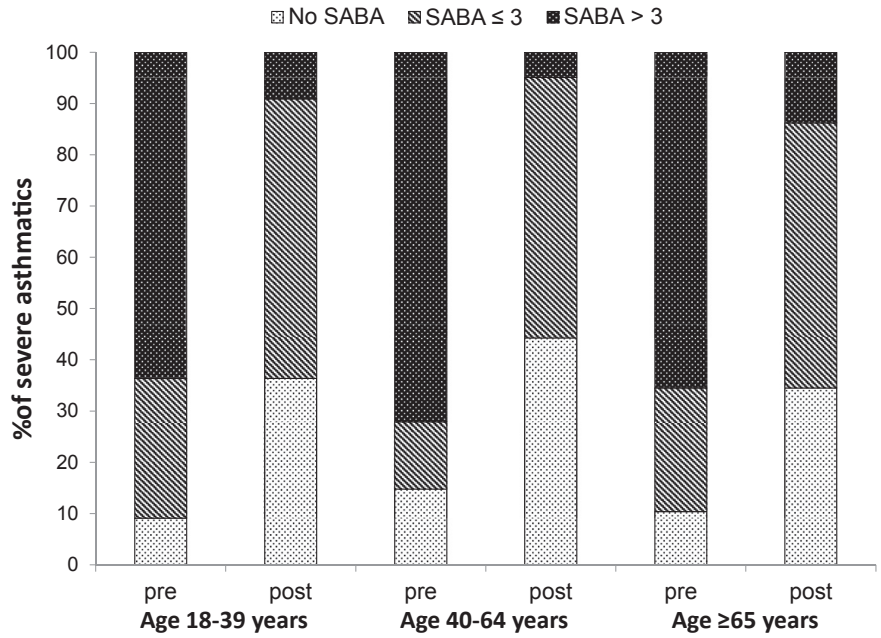

Fig. 5. Prevalence of subjects according to how often they used SABA (short-acting β_2-agonists) each week as a rescue medication reported in the month before (pre) Omalizumab treatment and in the month before (post) the beginning of this study in the 3 different age groups. Comparisons (test di Wilcoxon) of prevalence observed before and after treatment with Omalizumab: $p = 0.021$ between pre-and post-treatment in subjects aged 18–39 years; $p = 0.0001$ between pre-and post-treatment in subjects aged 40–64 years; $p = 0.0001$ between pre-and post-treatment in subjects aged ≥65 years. Comparisons (χ^2 test) of prevalence observed in subjects with different ages, before ($p = 0.631$) and after ($p = 0.641$) treatment with Omalizumab.

65 years (Table 2). Also overweight subjects showed a lower risk (OR = 0.176 [CI95% = 0.048–0.649], p = 0.009) for exacerbations at the end of the Omalizumab treatment period considered in this study, when compared to obese patients. No significant odd ratios were found for other covariates, in particular for allergic rhinitis, rhinosinusitis, nasal polyps, gastro-oesophageal reflux disease, hypertension, chronic heart disease, diabetes, osteoporosis and COPD.

Age still remained a risk factor for exacerbations (OR: 1.047 [CI95% = 1.010–1.086]; p = 0.012), also when considered as a continuous variable in the logistic model. Furthermore, the analysis without the 14 COPD patients confirmed that all younger subjects had the same lower risk for exacerbations in comparison with elderly patients after a long-term Omalizumab treatment (subjects aged 40–64:, OR = 0.199 [CI95% = 0.061–0.647] p = 0.007; subjects aged 18–39: OR = 0.096 [CI95% = 0.017–0.532], p = 0.007).

In addition, the linear regression model (Table 3) found a significant relationship among the three different age classes (18–39, 40–64 and ≥ 65 years) and the ACT score change obtained after Omalizumab. In fact, a significant reduced increase of ACT ($\beta = -1.081$; p = 0.041) passing from the younger to the older age classes, independently from all the confounding variables, was recorded. B value was −0.057 (p = 0.025) when age was considered as a continuous variable. Also when the linear regression model was applied without considering the 14 COPD patients, ACT values were negatively related with the three age classes considered ($\beta = -1.250$; p = 0.028). In addition, an ACT negative change was observed after Omalizumab treatment in overweight ($\beta = -3.035$; p = 0.0001) and obese ($\beta = -4.167$; p = 0.0001) subjects compared to normal weight individuals. Also a negative reduced ACT change was observed after Omalizumab in smokers ($\beta = -4.353$; p = 0.001). On the contrary, a positive relationship (a significant

Table 2
Risk (odd ratios) of having at least one exacerbation after Omalizumab treatment (compared to subjects that did not show any exacerbations).

	OR (95%CI)
[a]Patients with 18–39 years (vs those with >65 years)	0.133 [0.026–0.678]°
[a]Patients with 40–64 years (vs those with >65 years)	0.284 [0.098–0.826]^
[b]Age	1.047 [1.010–1.086]§
Overweight patients (vs obese subjects)	0.176 [0.48–0.649]*

Only significant covariates have been shown. °p = 0.015; ^p = 0.021; §p = 0.012; *p = 0.009.
Covariates included in the model were: sex, age (pre-Omalizumab), BMI, FEV_1, various sensitizations, IgE value, comorbidities (considering separately: hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD), smoking habits, asthma onset age, Omalizumab treatment duration, daily doses of ICS and montelukast use.
[a] Age was considered as a dichotomous variable.
[b] Age was considered as a continuous variable.

Table 3
Relationships (linear regression model), between ACT score changes after Omalizumab treatment and all parameters (below reported) measured for this study.

	β	p-value
[a]Classes of Age	−1.081	0.041
[b]Age	−0.057	(p = 0.025)
Obese subjects (vs normal weight patients)	−4.167	0.0001
Overweight subjects (vs normal weight patients)	−3.035	0.0001
Smokers (vs non-smokers)	−4.353	0.001
Subjects with nasal polyposis (vs others)	2.374	0.008

Only significant covariates have been shown.
Covariates included in the model were: sex, age (pre-Omalizumab), BMI, FEV_1, various sensitizations, IgE value, comorbidities (considering separately: hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD), smoking habits, age of asthma onset, Omalizumab treatment duration, daily doses of ICS and montelukast use.
[a] Age was considered as a dichotomous variable; a significantly reduced increase of ACT score after Omalizumab (−1.081; p = 0.041) was observed while passing from one age class to the other (18–39, 40–64 and ≥ 65 years).
[b] Age was considered as a continuous variable; a significantly reduced increase of ACT score after Omalizumab (−0.057; p = 0.025) was obtained for each year of age increase.

increase of ACT after treatment) was found in subjects affected by nasal polyposis ($\beta = 2.374$; $p = 0.008$) (Table 3).

4. Discussion

According to our long-term real-life study, Omalizumab has demonstrated to be efficient in improving asthma outcomes in all age brackets of uncontrolled severe asthmatics. In fact, FEV_1 and ACT increased whereas, exacerbations, ICS dosage and SABA used as rescue medications decreased significantly after approximately a 3-year Omalizumab treatment in all groups, independently of age. However, a reduced improvement in ACT and a lower rate of asthmatics without exacerbations were found in elderly asthmatics, when compared to younger patients, after a long-term treatment with Omalizumab. In addition, a lower risk for exacerbations during Omalizumab treatment was found in younger people when compared to elderly asthmatics. Also a negative relationship between ACT score change and age was detected, confirming that the effectiveness of Omalizumab may be reduced in the elderly. Another previous real-life study had found that 24% of asthmatics in treatment with Omalizumab had shown a poor asthma control [17]. These subjects were older when compared to well-controlled asthmatics, confirming that just the elderly may have a more difficult disease control even when treated with Omalizumab. This would suggest a reduced response to treatment in elderly patients or a more severe asthma more difficult to treat in these categories of subjects. There is no clear evidence supporting a lower efficacy of asthma therapies in older subjects [8,18], whereas, it is more probable that a poor response may depend on a different asthma phenotype in the elderly, characterized by a greater disease severity. According to our study, asthmatics over 65 years, showed a higher BMI (more numerous overweight/obese subjects), a greater number of comorbidities and a more advanced asthma onset age, when compared to younger subjects. These different characteristics may increase disease severity and therefore reduce the response to treatment in the elderly. Concerning a possible influence of high BMI on Omalizumab treatment in the elderly (where a higher body weight is more frequent), we found that overweight/obesity status, independently of other factors, has determined a reduced response in terms of ACT score and an higher risk for exacerbations (compared to a lower weight status) after Omalizumab treatment. Therefore, obesity can be an important factor that may have influenced the reduced response to Omalizumab in the elderly asthmatics of our study in terms of ACT score and number of exacerbations. In fact, overweight/obese status, with an increased subcutaneous and visceral abdominal fat mass, which is a characteristic of elderly subjects, is a risk factor for a higher airway hyperresponsiveness (AHR), lung function decline and asthma risk [19–25]. Furthermore, in obesity, lung volume and tidal volume are reduced, thus promoting airway narrowing [21,25,26]. Obesity also leads to a state of low-grade systemic inflammation (increased leptin, TNF-α, IL-6, TGF- β1, adiponectin and C-reactive protein) that may act on the lungs to aggravate asthma [25,26]. In fact, the proportion of obese subjects increased with asthma severity, reaching the peak in the highest asthma severity step [27]. Furthermore, several studies showed an inverse relationship between BMI categories and reduction in asthma control, in response to all controller therapies (ICS, antileukotrienes and ICS plus long-acting β agonist in combination) [26–30].

In addition, overweight and obesity are associated to other comorbidities (glucose intolerance, dyslipidemia, hypertension, type 2 diabetes, kidney failure, osteoarthritis, others) which can lead, in general, to further morbidity and mortality [31]. The comorbidity burden is significantly associated with asthma-related quality of life, unscheduled asthma care, emergency department visits, asthma hospitalizations, or the 30-day fatality rate following asthma hospitalizations [16]. Furthermore, comorbidities are associated with an ageing population; they negatively affect health outcomes and are associated with asthma in these subjects [9–11]. In fact, according to our study, comorbidities such as hypertension, chronic heart disease, diabetes, gastro-esophageal reflux and osteoporosis are more prevalent in old age, making the disease more severe and thus probably influencing the reduced response to Omalizumab treatment in the elderly. In confirmation, some researches have shown that poor asthma control, measured as reduced ACT, was associated with asthma-related comorbid diseases in real-life [14,17,32].

In particular, we observed an increased number of elderly subjects affected by hypertension which may be a marker of asthma severity in older asthmatic patients. In fact, according to recent studies [33], asthmatic subjects with comorbid hypertension display evidence of enhanced asthma morbidity.

Unfortunately, when we applied logistic and regression models we did not find any associations between comorbidities (singularly analyzed) exacerbation reductions and improvements of ACT score, did not apparently confirm a comorbidity influence on the Omalizumab treatment response. This is probably due to the number of patients recruited for this study, not sufficiently large (above all in elderly group) to reveal a possible relation between comorbidity and poor response to treatment.

Smoking was another factor that has determined a reduced increase in ACT after Omalizumab influencing thus the efficacy of treatment. A meta-analysis study had already shown that smoking asthmatics show a reduced response to inhaled corticosteroids [34] with a consequent poor asthma control. This lower asthma control may be due to AHR and airway inflammation increases (especially in the elderly) induced by smoking [19,35–37]. In fact, smoking may induce changes in airway inflammation with a progressive development of a higher degree of neutrophilic inflammation in asthmatics [38]. These changes can progressively worsen asthma by inducing also a concomitant COPD in 27.4% of asthmatic smokers [39]. A state of neutrophilic inflammation (and therefore COPD complication) may lead to an increased steroid resistance and an accelerated loss of lung function owing to tissue destruction also in asthma-COPD overlap [40]. Consequently, these alterations would suggest un-treatability or at least under-responsitivity to anti-inflammatory treatment of these patients. Therefore, a co-existence with COPD might make asthma poorly responsive to Omalizumab and therefore it might have influenced our results. However, our analysis did not highlight that the concomitant COPD was not a risk factor for exacerbations nor that it was associated to a reduced improvement of ACT score after Omalizumab. Also the analysis without asthma-COPD overlap patients pointed out the same a reduced improvement of symptoms and a higher risk for exacerbations in the elderly. This would indicate that a COPD overlapping may not influence the effectiveness of asthma treatments. Unfortunately, the small number of patients with asthma-COPD overlap in the elderly group does not permit us to confirm this hypotheses. On the contrary, in our real-life study, also some patients with severe asthma worsened by COPD showed a significant improvement, even if lower in comparison with younger patients, after omalizumab thus suggesting a possible role of anti-IgE treatment also in severe asthma-COPD overlap. Other ACOS case reports confirmed a positive result with Omalizumab [41,42] Such efficacy may be due to the effect of this drug on the asthmatic inflammatory component, even in the presence of a concomitant COPD-induced inflammatory component.

According to the regression model, a significant increase in ACT was observed in patients with severe asthma associated to polyposis. This suggests that Omalizumab may be efficacious also in nasal

polyposis, probably by acting on local activation of polyclonal IgE [43,44]. In fact, there is some evidence that Omalizumab may improve various nasal polyposis outcomes [43,44]. This nasal complication may induce a worsening of airway inflammation and thus of asthma [44,45]. In fact, nasal polyps and asthma represent the most severe form of unified respiratory tract disease. Therefore, an improvement of nasal polyposis may have also repercussions on airway inflammation and therefore on asthma symptoms.

One more aspect of our study is the proof that asthma onset age was higher in older subjects and that it may have induced the lower efficacy of Omalizumab. Asthma onset age is used to distinguish different adult asthma phenotypes. When starting in adulthood, asthma differs from childhood-onset as regards high symptom scores, poor quality of life, the need for high-intensity treatment, low/fixed lung function and high exacerbation rate. Furthermore, patients with severe adult-onset are more often females, non-atopic, with more nasal symptoms, nasal polyposis, higher exhaled nitric oxide levels, blood neutrophil counts and sputum eosinophilia [46,47]. All these features, which are different in younger subjects, may explain the reduced effect of Omalizumab in the elderly. Actually, the development of late-onset adult asthma may be also the clinical consequence of immunosenescence that would lead to decline in functionality of the immune system with increasing age [48–51]. This age-related process determines a progressive impaired mucociliary clearance, changes in airway neutrophil, eosinophil, and mast cell numbers and function over an altered antigen presentation and decreased specific antibody responses [50]. Furthermore, this immunosenescence and its concomitant chronic low grade systemic “inflamm-aging” may contribute to the development and progression of pulmonary disease in older individuals [47,50]. Therefore, immunosenescence may favor a neutrophilic inflammation determining a more severe disease and less effective asthma treatments in the elderly [51]. In our study, we found that aging was negatively related to Omalizumab treatment response in terms of increase in ACT score and reduction of exacerbations after therapy, independently from all confounder factors considered by this study: sex, BMI, FEV_1, sensitizations, IgE value, comorbidities, smoking habits, asthma onset age, Omalizumab treatment duration, daily doses of ICS and montelukast use. This suggests that a reduced response to treatment in the elderly may be simply due to a “senescence process” progressing with aging, independently from other factors, that favors a more severe asthma development through immunological/inflammatory events different from the ones seen in younger asthmatics. Therefore, comorbidities may be part of a global “senescence process” together with other pulmonary diseases and, for this reason, comorbidity and asthma should only be associated as one is not the cause of the other.

5. Conclusion

In conclusion, adding Omalizumab can improve uncontrolled step-4/5 asthma in a real-life setting independently of age. However, improvement may be poorer in the elderly. Such lower response to Omalizumab treatment may be due to an association with comorbidities, in particular hypertension, overweight/obese status, smoking habits and a more advanced asthma onset age. On the other hand, just the “senescence process” (progressive with age) may be responsible for the lower efficacy of Omalizumab in the elderly.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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