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

Effects of Omalizumab on severe asthma in the elderly: a real life study.

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Running Head: **Omalizumab and elderly severe asthma**

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Abstract

Background Asthma in the elderly seems to be more severe compared to asthma in younger patients, with a possible reduced responsiveness to treatment. The aim of this study was to evaluate long-term effects of Omalizumab in elderly asthmatics in a real-life setting.

Methods: 105 consecutive severe asthmatics (step 4-5 according to GINA criteria; mean FEV_1:66±15.7%) on treatment with Omalizumab for at least 1 year (mean 35.1±21.7 months) were included into the study and divided into 3 groups according to the age at the onset of Omalizumab treatment: 18-39, 40-64 and ≥65 years.

Results: Older subjects differed from the other groups for number of comorbidities, prevalence of overweight/obese subjects and for later asthma onset. A significant and similar reduction of controller therapy and use of SABA on demand was observed in the three groups during omalizumab therapy. FEV_1 increased significantly and similarly in all the groups. Asthma Control Test (ACT) improved significantly ($p < 0.001$) in the three groups , increasing from 15 [12-18] to 24 [22-25] in the younger, from 14 [10-16] to 21 [20-23] in the 40-64 years group and from 15 [12-16] to 20 [18-22] in the elderly, the improvement being lesser than in the other groups ($p = 0.039$). The decrease in asthma exacerbation was significant in all the groups, but the percentage of patients free of exacerbations was higher in the younger (76.9%) compared to middle aged patients (49.2%) and elderly(29%) ($p=0.049$).

Conclusion: Omalizumab improved all asthma outcomes independently of age, but the magnitude of the effects observed in the elderly were significantly lesser than in the other age groups.

Introduction

Severe asthma is defined as the requirement for high-intensity treatment to obtain a disease control (1). However, despite using high doses of inhaled corticosteroids (ICS), bronchodilators and anti-leukotriens, we sometimes fail to achieve asthma control. In this case, adding Omalizumab to treatment permits us to improve the disease control. In fact, Omalizumab (Xolair®) is a recombinant DNA-derived humanized monoclonal antibody indicated as an add-on therapy in patients aged ≥ 6 years with severe persistent allergic asthma uncontrolled at treatment step 4 or 5 according to guidelines GINA (2). Omalizumab 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 in terms of improving lung function and quality of life, achieving asthma control and reducing symptomatology, severe exacerbations, healthcare resource utilizations, hospitalizations, emergency department visits and reducing or discontinuing other asthma medications thus confirming, complementing, and extending evidence from randomized trials (3,5).

However, in the various studies performed to test the effectiveness of Omalizumab, elderly patients are under-represented. Therefore, it is not well clear if Omalizumab is able to improve significantly asthma control in severe asthmatics older than 65 years. Only one study observed an improvement of asthma outcomes after a short follow-up (4 months) of Omalizumab treatment in asthmatics older than 50 years similarly to patients younger than 50 years (6). However, the doubt about Omalizumab effectiveness in patients older than 65 years, above all in the long term, still remains. In fact, there are data suggesting that asthma in older adults is phenotypically different from asthma in younger patients. Some pathophysiological mechanisms of elderly asthma are different from those seen in young asthmatics and these differences may influence the clinical course, asthma outcomes and treatment response in this population. In fact, the elderly have lower post-bronchodilator FEV_1%, more exacerbations and risk of first severe exacerbation is increased by 55.3% when compared to younger patients (7). Asthma in the elderly seems to represent a specific phenotype characterized by more severe, but often less perceived, airway obstruction, a neutrophilic or mixed-type of airway inflammation and frequent comorbidities (8,9). Older asthmatics are often characterized by long-standing asthma that has more severe airflow limitation and less complete reversibility (or even irreversibility) than in patients with late-onset asthma (10). In fact, airways remodeling and a possible coexisting COPD can determine a greater asthma severity in the elderly (11). Older patients with asthma have significantly increased percentages of sputum neutrophils (12). This pattern is a characteristic of intrinsic asthma with neutrophilic inflammation that may be associated to a more severe obstructive disease and a poor response to treatment (8-10). In addition, elderly subjects usually have multiple chronic illnesses that can be also associated with poor asthma outcomes (13-15). Therefore, severe asthma in the elderly may be more serious and thus more difficult to treat in comparison to severe asthma in younger patients. Likely, the advanced age itself may also influence the response to Omalizumab.

Therefore, the aim of this study was to assess the effectiveness of long-term Omalizumab treatment in a real-life setting in patients over 65 with severe uncontrolled asthma.

Materials and Methods

Eighteen Italian Asthma Units were involved in this retrospective study. Data of at least 3 consecutive severe asthmatics (step 4-5 according to GINA criteria) (2) in treatment with Omalizumab, for at least 1 year, were requested from each Center. All recruited patients should have shown a poor disease control with an ICS therapy associated to long-acting bronchodilators and Montelukast for which it was necessary to add Omalizumab. Data were extracted from each patient's clinical record and recorded in a previously agreed form. Information relative to demographic data, allergic sensitization *(Dermatofagoides pteronissinus* and *D. farinae*, Grass mix, *Parietaria*, *Olea europaea*, *Cupressus sempervirens*, *Betula pendula*, *Alternaria tenuis, Aspergillus f.* and dog-cat dander), IgE values, the presence of rhinitis, sinusitis, nasal polyposis, other comorbidities (hypertension, chronic heart disease, diabetes, osteoporosis, gastro-esophageal reflux, COPD, obesity), smoking habits and body mass index (BMI) obtained before the onset of Omalizumab treatment were required for each patient. Furthermore, age of asthma onset, Omalizumab dosing and period of treatment with anti-IgE were required in the form. For the purpose of the study, the evaluation, before and after Omalizumab treatment, of FEV_1, FEV_1/FVC, Asthma Control Test (ACT), number of moderate/severe exacerbations registered in the previous year, ICS doses, treatments with LABA,LAMA, Montelukast and how many times a week SABA (as rescue medication) was used, were also considered. It was also evaluated if the treatment was in general stable or reduced after using Omalizumab. The period of data collection was November 2014 – November 2015. At the end of such period, 105 severe asthmatics were recruited.

For the objective of our study, these patients were divided into 3 groups on the basis of age observed at the onset of Omalizumab treatment: subjects aged 18-39, 40-64 and ≥65 years. Then all data of each group were compared.

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 number of exacerbations and daily dosage of ICS reported in the year before using Omalizumab and during the last year of treatment with anti-IgE (before our 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 a documented evidence were considered. Diagnosis of asthma-COPD overlap was established when, in presence of chronic

cough/phlegm and smoking history, hyperinflation and reduced single breath CO diffusion test (DLCO) <80% was assessed by spirometry and/or central-panlobular emphysema was seen by high resolution computed tomography.

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.

Comparison of continuous variables among the age groups was 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. A logistic binary regression model, corrected for sex, BMI, FEV_1, sensitizations, IgE value, comorbidities, smoking, age of asthma onset, Omalizumab treatment duration, daily dose of ICS and montelukast use, was applied with the purpose to test if zero setting of exacerbations was an independent and different risk factor in the various age brackets (18-39,40-64 and ≥65 years). Furthermore, a linear regression model, corrected for all parameters, above reported, was also performed to test if ACT changes after Omalizumab treatment were independently related to the three classes of age considered (18-39,40-64 and ≥65 years).

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

Results

Asthmatics aged between 18 and 39 years were 13 (12.4% of all patients; mean FEV_1: 67.2±12.4%), whereas patients aged between 40 and 64 years were 61 (58.1% of all patients; mean FEV_1: 65.6±16%) and those aged ≥65 years were 31 (29.5% of all patients; mean FEV_1: 66.2±16.7%). In Table 1, are reported and compared data observed in the three groups with different ages. BMI resulted higher ($p=0.049$) in subjects with medium and older age. No difference in number of allergen sensitizations was found in three groups. Furthermore, no differences were observed in total IgE values (evaluated before beginning the Omalizumab therapy), doses and time (months) of

anti-IgE drug treatment. Also the number of subjects in treatment with ICS, long-acting bronchodilators and montelukast (used before adding Omalizumab) was similar in the three groups. Anyhow, the number of asthmatics with more comorbidities was obviously higher in those with older age.

In figure 1 are reported median FEV_1% values measured before (pre) and after (post) adding Omalizumab. Percentage pre-values (70 [60-76.6]; 68 [55-75]; 67 [58-79]; p=0.838; figure 1/A) and post-values (82.1 [73-88]; 82 [66-93]; 80 [71-92]; p=0.906; figure 1/B) measured in asthmatics with younger, medium and older age (respectively) were similar. Whereas, FEV_1 values, measured after treatment with Omalizumab, improved significantly (p<0.001; comparing pre-post) and similarly in each group. Also ACT values (figure 2), measured after Omalizumab treatment, improved significantly (p<0.001; comparing pre-post – figure 2 A and B) in each group (pre values: 15 [12-18]; 14 [10-16]; 15 [12-16]; post-values: 24 [22-25]; 21 [20-23]; 20 [18-22]; measured in subjects with younger, medium and older age respectively). However, the improvement of ACT observed after Omalizumab was lower in asthmatics over 65 years (20 [18-22]) when compared with younger subjects aged 18-39 years (24 [22-25]; p=0.039; figure 2).

There was a significant reduction in the number of exacerbations after Omalizumab treatment in each group (Figure 3; p<0.0001). The number of exacerbations recorded before the ant-IgE treatment was similar in the three groups, but different after Omalizumab treatment. In fact, no exacerbations were obtained in 76.9% of younger subjects, in 49.2% of patients with medium age and only in 29% of older asthmatics (p=0.049). ICS doses decreased significantly and similarly after anti-IgE treatment in each group (p<0.01; figure 3). We also observed a significant and similar reduction of SABA used as a rescue medication in all groups (Figure 4).

Having found a difference in number of exacerbations among 3 groups, we applied a logistic model considering as dependent variable zero setting of exacerbations corrected for sex, BMI,FEV_1, sensitizations, IgE value, comorbidities, smoking habits, age of asthma onset, Omalizumab treatment duration, daily doses of ICS and montelukast use. Younger subjects showed a significantly higher odd ratios to develop zero exacerbations (subjects aged 40-64: 3.52 [1.21-10.23], p=0.021; subjects aged 18-39: 7.52 [1.47-38.39], p=0.015) in comparison to subjects over 65 years. In addition, having found a lower ACT increase in the elderly, we applied a linear regression model (corrected for all the above said variables) to evaluate the relationship among the three different classes of age and the change of ACT obtained after Omalizumab. In

confirmation to what observed above, we found a significantly reduced increase of ACT (-1.070; p=0.046) passing from one class of age to the other, independently of all the confounding variables.

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 in the previous year were found in elderly asthmatics, when compared to younger patients, after a long-term treatment with Omalizumab. In addition, a previous real-life study found that 24% of asthmatics patients in treatment with Omalizumab showed a poor asthma control (16). These subjects were older when compared to well-controlled asthmatics, confirming that just the elderly may have a more difficult control of the disease even 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 (7,17), 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. In fact, 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. In fact, overweight/obese status, with an increased subcutaneous and visceral abdominal fat mass, which is a characteristics of elderly subjects, is a risk factor for a higher airway hyperresponsiveness (AHR), lung function decline and risk of asthma (18-24). Furthermore, in obesity, lung volume and tidal volume are reduced, thus promoting airway narrowing (20,24,25). 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 (24,25). In fact, the proportion of obese subjects increased with asthma severity step, reaching the peak in the highest asthma severity step (26). 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) (25-29). 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 level and number of exacerbations.

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 (30). The comorbidity burden is significantly associated with asthma-related quality of life, unscheduled asthma care, emergency department visit, asthma hospitalization, or the 30-day fatality rate following asthma hospitalization (15). Furthermore, comorbidities are associated with an ageing population; they negatively affect health outcomes and are associated with asthma in these subjects (8-10). 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 thus influencing the reduced response to treatment with Omalizumab 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 (13,16,31).

In particular, we observed an increased number of elderly subjects affected by hypertension that may be a marker of asthma severity in older asthmatic patients. In fact, according to recent studies (32), asthmatic subjects with comorbid hypertension display evidence of enhanced asthma morbidity.

Another 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. Asthma starting in adulthood differs from childhood-onset as regards asthma 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 asthma are more often females, non-atopic, with more nasal symptoms, nasal polyposis, higher exhaled nitric oxide levels, blood neutrophil counts and sputum eosinophilia (33,34). All these features, 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 (35-38). 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 (37). Furthermore, this immunosenescence and its associated chronic low grade systemic "inflamm-aging" may contribute to the development and progression of pulmonary disease in older individuals (34,37). Therefore, immunosenescence may favor a neutrophilic inflammation that determines a more severe disease and less effective asthma treatments in the elderly (38). In our study, we found that aging was negatively related to Omalizumab treatment response in terms of increase in ACT and reduction of exacerbations after therapy, independently to all confounder factors considered by this study: sex, BMI, FEV_1, sensitizations, IgE value, comorbidities, smoking habits, age of asthma onset, Omalizumab treatment duration, daily doses of ICS and montelukast use. This suggest that a reduced response to treatment in the elderly may be simply due to a "senescence process" progressing with aging, independently of other factors, that favour a more severe asthma development through an immunological/inflammatory process different from the one seen in younger asthmatics. Therefore, comorbidities may be part of a global "senescence process" together with other pulmonary diseases. According to this concept, comorbidity and asthma should only be associated as one is not the cause of the other.

In conclusion, adding Omalizumab can improve uncontrolled step-4/5 asthma in a real-life setting independently of age. However, improvement may be lower in the elderly. This poorer response to Omalizumab treatment may be due to an association with comorbidities, in particular hypertension and overweight/obese status, and to 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.

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Table and Figures Legends

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

Figure 1: FEV_1 values measured before (Pre) and after (Post) Omalizumab treatment.

Comparison 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

Figure 2: Asthma Control Test (AC) values measured before (Pre) and after (Post) Omalizumab treatment.

Comparison 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**; post-values p=0.039.**

Figure 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 groups with different ages.

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=0.001 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.

Figure 4: Prevalence of subjects treated with different ICS levels used before (pre) and after (post) at least 1 year of Omalizumab in the 3 groups with different ages

Low dose of ICS: <500 µg equivalent to bechlometasone; Medium dose of ICS: 500-1000 µg equivalent to bechlometasone; High dose 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 age, before (p=0.369) and after (p=0.757) treatment with Omalizumab.

Figure 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 groups with different ages.

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 age, .before (p=0.631) and after (p=0.641) treatment with Omalizumab