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Asthma control in severe asthmatics under treatment with omalizumab: A cross-sectional observational study in Italy

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ABSTRACT

Few data are available on the proportion of asthmatics achieving a good asthma control (according GINA guidelines) and on the level of airway inflammation during omalizumab treatment.

The aim of this cross-sectional national observational study was to assess the level of control (according to GINA guidelines) achieved in a group of asthmatics on omalizumab treatment, and to characterize the factors that influence the lack of control.

We studied 306 asthmatics under omalizumab treatment for a median of 32 months (range 4–120). The level of control according to GINA was good in 25.2%, partial in 47.1% and poor in 24.5% of patients (data were missing for the remaining 3.2%). Comparison between poorly controlled and partially or well controlled asthmatics showed a statistically significant higher prevalence of some comorbidities in the first group, namely obesity, gastro-oesophageal reflux disease (GORD), aspirin intolerance and mental disorders (all $p < 0.001$). Similarly, asthmatics with at least one exacerbation in the last year showed a significantly higher prevalence of obesity, chronic rhinosinusitis, nasal polyps, GORD, and aspirin intolerance (all $p < 0.05$) than patients without exacerbations. When we selected patients without relevant comorbidities (upper airways disease, GORD, obesity, aspirin intolerance) and not currently

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smoking ($N = 73$), the percentage of well or partially controlled asthmatics was significantly higher than in patients with comorbidities (84.9% vs 71.1%, $p = 0.02$); the rate of asthmatics without exacerbations in the last year was also higher (73.6% vs 51.1%, $p = 0.001$).

During omalizumab treatment, a high percentage of asthmatics obtain a good or partial control of asthma. Comorbidities are associated with the lack of asthma control and persistence of exacerbations.

1. Introduction

Patients with severe asthma represent one of the major problems in the management of this disease. Although severe asthmatics account for only 5%–10% of asthma population, they are responsible for more than 80% of the total health cost for asthma [1]. These patients are usually treated with high-dose inhaled corticosteroids (ICS) plus long-acting-beta2agonist (LABA), often associated with other drugs (montelukast, theophylline, tiotropium), but despite a high burden of pharmacologic treatment the control of the disease is only occasionally obtained and the patients continue to experience diurnal and nocturnal symptoms, frequent exacerbations requiring oral steroids and/or hospitalization, and poor quality of life with substantial limitations in daily life activity [2].

In recent years, omalizumab (Xolair), a monoclonal antibody directed vs human IgE, has been introduced for the treatment of severe allergic asthma. The hypothesis was that minimizing free serum IgE concentration and then binding to IgE receptor-bearing inflammatory cells, the whole allergic cascade would be blocked at the beginning, thus leading to improvement of the airway inflammatory pattern and potentially to the airway remodeling [3]. In this very selected target population the high cost of the treatment is balanced by a high efficiency in patients with a high asthma-related burden, leading then to a favorable cost-effectiveness ratio [4]. Registrative and post-registrative studies have largely demonstrated that omalizumab induced a great reduction in asthma exacerbations (particularly those associated to emergency department access or hospitalization) and a substantial improvement in quality of life [5–7].

After the entry on the market, several observational studies have been published, showing the high efficacy of omalizumab in real life. After the first observations performed in France, Germany and Belgium [8–10], many other regional studies have been performed, with the aim of describing the outcome of asthma in samples of severe asthmatics treated with omalizumab: while the majority of these studies included relatively small groups of patients followed for few months or years, only few national or international registries have evaluated the outcome of asthma after long-term treatment with omalizumab (e.g. up to 6 years) in hundreds of patients, confirming in the real life the high efficacy of omalizumab in terms of reduction of symptoms, exacerbations, pharmacologic burden, and improvement in quality of life in adults [11–17] and in children [18]. However, none of these studies have evaluated the real asthma control level according to GINA, or some markers of airway inflammation, such as sputum or blood eosinophils or exhaled nitric oxide (eNO).

In Italy, omalizumab has been available since 2007, and its use is limited to patients with severe uncontrolled asthma associated with allergic sensitization to perennial allergens and a well defined ratio between serum IgE and body weight. A first multicenter observational study analyzed the data of the first group of Italian patients ($N = 142$) treated from at least 4 months and up to 12 months with omalizumab [19]. Data were limited to the informations included in the AIFA register (number of exacerbations, concomitant medication, global assessment of efficacy). The results of this study confirmed the very low number of exacerbations during omalizumab treatment and the high level of efficacy obtained in almost all the examined patients.

Some years after this the first observation, Italian researchers aimed to verify the current level of real asthma control in a large, unselected sample of severe allergic asthmatics treated for several years with omalizumab, with the attempt to include some more standardized measurements of the level of asthma control, pulmonary function measurements and biomarkers of airway inflammation. In particular, we would like to assess the percentage of these patients who gained a well or a partial control of asthma during omalizumab treatment, and if this was associate with specific characteristics of the patients.

2. Patients and methods

This cross-sectional observational study was performed in 26 italian centers (the list of the contributors is reported in the Appendix). All patients attending the centers for the regular administration of omalizumab were asked to participate to the study. The study protocol was approved by the Ethic Commitee of the Coordinator Centre (Ethic Commettee of the University Hospital of Pisa, protocol FPR0001 no. 3436, approved 10 nov 2011) and later on by all Ethic Committees of the different Italian centers. Informed consent was obtained from all participants.

Patients underwent a detailed questionnaire in order to analyze the characteristics of asthma at the time of the observation. Several sections were considered: a) anthropometric data, including age, gender, body mass index (BMI), education level and area of residence; b) clinical history of asthma: age of onset, skin sensitivity, serum IgE levels, methods of diagnosis; c) current level of asthma treatment (with great detail on the dose of the different ICS and on whether all treatments were left unmodified, increased or reduced after the beginning of omalizumab treatment), duration of the omalizumab treatment, adherence to the treatment, and assessment of the correct use of the inhalers; potential local or systemic side effects of omalizumab treatment were also investigated; d) number and severity of comorbidities (allergic rhinitis, rhinosinusitis, nasal polyps, gastro-oesophageal reflux disease (GORD), aspirin intolerance, psychiatric disorders, obstructive sleep apnea, etc), with the evaluation whether during omalizumab treatment these comorbidities improved or not; e) exposure to pollutants or irritants, including smoking habit; f) number and characteristics of exacerbations, both during the whole period of omalizumab treatment and in the last year; number of unscheduled visits to GPs and pulmonary specialists, number of hospitalizations or emergency room accesses, both before and after omalizumab treatment, number of days of oral corticosteroids use, number of days of work or school lost owing to the disease. **All these informations were collected by the record forms of each patient, where they were reported both in the pre- and in the post-omalizumab treatment period. As regards comorbidities, only those which had a documented demonstration (e.g. report of an ENT evaluation or CT scan of**

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paranasal sinus, gastroscopic assessment, psychiatric assessment, etc) were considered.

Additional questions were related to the assessment of asthma control according to GINA, taking in consideration the frequency of diurnal and nocturnal symptoms, rescue medication use, limitation in daily life in the last month, combined with the presence of exacerbations in the last year and FEV1 value; this allowed the distinction of patients in well controlled, partly controlled and uncontrolled. ACT questionnaire was also filled.

Pulmonary function tests, including FEV1 pre- and post-bronchodilator, were obtained. Reference values were derived from Quanjer et al. [20].

As biomarkers, blood eosinophil counts and exhaled nitric oxide (eNO) concentration were obtained in part of the examined patients. Exhaled nitric oxide was measured with different analyzers, but in all cases following the international recommendations [21]. Additional measurements (AQLQ questionnaire, and static lung volumes, and sputum eosinophil percentages) were obtained in a minority of the examined patients.

Data are presented as mean ± SD or as median and range, for normally or non-normally distributed measures, respectively. Statistical analysis was performed using the SPSS package. ANOVA, Mann Whitney and Kruskal Wallis tests were used when appropriate for the comparison among different groups of patients. Chi square was also computed for the distribution of the exacerbations before and after omalizumab treatment. A p value lower than 0.05 was considered statistically significant.

3. Results

Three hundred six patients were enrolled (Table 1). As a median, each center collected data from 12 patients (from a minimum of 4 to maximum number of 22). Mean age was approximately 52 yrs, two third of the patients were female, and approximately 30% were ex-smokers or current smokers. Asthma onset was at 26 yrs as a median, but a large variety from childhood to adult-onset asthma was reported. Rhinitis was referred by two third of the sample, and most of them had also sinusitis with or without nasal polyps. Other comorbidities were widely reported (obesity, GORD, aspirin intolerance, psychiatric disorders). The large majority of these patients were sensitized to house dust mites, while only 14% were sensitized to moulds. Multiple allergic sensitivity was reported by 66.8% of the patients.

Objective measurements of asthma control (including inflammatory biomarkers) in the whole group are reported in Table 2. Mean FEV1 was 74.6% pre-bronchodilator and 76.6% post-bronchodilator. The level of asthma control according to GINA (taking into account the frequency of diurnal and nocturnal symptoms, use of rescue medication, limitation in daily life in the last month, FEV1% predicted, and frequency of exacerbations in the last year) was defined as good control in 25.2%, and partial control in 47.1% of patients; therefore, only 24.5% of patients were still uncontrolled despite the treatment with omalizumab and other additional drugs (for a minority of the patients, asthma control was not evaluable for some missing informations). This was reflected also by the value of ACT, which was 21 as a mean, with a wide range between 6 and 25. The only markers of inflammation available were blood eosinophils (available in 191 patients, 62.4%, and higher than 300 cells/ul in 86 patients, 45%) and exhaled nitric oxide (available only in 131 patients, and higher than 25 ppb in 48.1% of the examined patients).

The duration of treatment with omalizumab was 32 months as a median, with a wide range, from 4 to 120 months. As for the use of concomitant medications, ICS were used in 96% of patients (in 53.3% of them at high doses) and LABA in 90.7% of patients, while in lower percentages montelukast (55.2%), theophylline (9.5%) and/or tiotropium (12.1%) were used. Only 7.5% of patients still remained on long-term oral corticosteroids. Furthermore, the length of OCS use for acute exacerbations was low (9.6 days in the last year).

Number of exacerbations (defined as episodes of asthma worsening requiring oral corticosteroid use) in the last year of omalizumab treatment, and the number of emergency room accesses or hospitalization during the entire treatment period were recorded, and compared with similar data related to the period before omalizumab treatment (Fig. 1). There was a strong significant reduction in the annual rate of exacerbations during omalizumab treatment ($p < 0.001$ for the distribution of asthma exacerbations before and after omalizumab treatment by χ^2): more than 50% did not report any exacerbation in the last year, and only 4.4% reported 2 or more exacerbation in the last year. Finally, few patients had emergency department accesses and hospitalizations for asthma

Table 1
Clinical characteristics of the patients.

General characteristics	
Number of subjects	306
Age, years	52 ± 13,7
Gender, M/F %	36.9/63.1
Smoke, Yes/Ex/No %	3.6/27.1/68.6
PY (ex + current smokers)	10 (0.5–67.5)
BMI	26.4 (16.7–46.8)
Familiarity for asthma, *n*(%)	134 (45.4)
Age of onset, years	26 (0–75)
Total serum IgE, UI/ml	330.7 (26–2353)
Comorbidities	
Rhinitis, *n* (%)	200 (66.2)
Sinusitis, *n* (%)	100 (34.2)
Nasal polyps, *n* (%)	77 (25.8)
Aspirine intolerance, *n* (%)	64 (22.1)
Obesity, *n* (%)	69 (22.6)
GORD, *n* (%)	108 (36.6)
Mental disorders, *n* (%)	24 (8.2)
Sensitization to allergens	
House dust mites, *n* (%)	242 (84.6)
Dog, *n* (%)	57 (20.3)
Cat, *n* (%)	66 (23.5)
Moulds, *n* (%)	39 (14.2)
Parietaria pollen, *n* (%)	86 (31.2)
Grass pollen, *n* (%)	102 (37)
Pollen from trees, *n* (%)	106 (37.6)
Polyallergics, *n* (%)	183 (66.8)

Data are reported as mean ± SD, or median and range.
PY = packs year; BMI = body mass index; GORD = gastroesophageal reflux disease.

Table 2
Functional and inflammatory parameters and control of asthma in the examined patients.

Lung function	
Pre-BD FEV1, L	2.07 ± 0.79
Pre-BD FEV1, % of pred.	74.6 ± 20.5
Post-BD FEV1, L	2.17 ± 0.76
Post-BD FEV1, % of pred.	76.6 ± 20.1
Inflammatory markers	
FeNO (n = 131), ppb	24 (0–246.6)
FeNO>25 ppb, *n* (%)	63 (48.1)
Blood eosinophils (n = 191), *n*/mm3	271.8 (0–1570)
Blood eosinophils, %	4.2 (0–22.5)
Control of asthma (according to GINA)	
Poorly controlled, *n* (%)	75 (24.5)
Partially controlled, *n* (%)	144 (47.1)
Well controlled, *n* (%)	77 (25.2)
ACT score	21 (6–25)
ACT score ≥20, *n* (%)	202 (66)

BD = bronchodilator; FEV1 = forced expiratory volume in the 1st second; FeNO = fractional exhaled nitric oxide; ACT = asthma control test.

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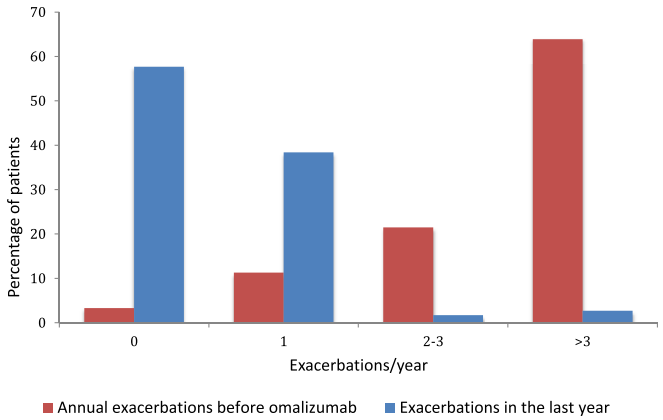

Fig. 1. Distribution of the number of exacerbations in the year before omalizumab treatment (red columns) and in the last year of omalizumab treatment (blue columns). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

during omalizumab treatment (7.5% and 6.5% respectively) compared to pre-omalizumab treatment (57.2% and 45.7%, respectively), as well as requirement for intensive care treatment (0.3% vs 3.6%, after and before omalizumab treatment, respectively).

In order to assess the potential factors which may reduce the probability of reaching a good or partial asthma control during omalizumab treatment, we divided the patients according to the level of asthma control in the previous month (Table 3). Patients who reached a good asthma control were younger and with an earlier onset of the disease. Uncontrolled patients had a lower pulmonary function, as expected, and a higher rate of some comorbidities (aspirin sensitivity, obesity, gastro-oesophageal reflux disease [GORD], and mental disorders). No significant difference was observed among groups with different asthma control according to the level of blood eosinophils and FeNO concentrations. Uncontrolled and partially controlled patients were more frequently treated with high dose ICS, LABA, OCS, and tiotropium. In addition, no difference among groups was observed as regards the type of allergen sensitivity.

We also divided patients according to the presence of at least one exacerbation in the last year of omalizumab treatment (Table 4). Patients who reported at least one exacerbation in the last year were 125 (42.8% of the patients with available data); age, gender, asthma duration and length of treatment with omalizumab of these patients were similar to those without exacerbations. Patients with exacerbations had significantly lower pulmonary function, higher BMI, and higher rate of comorbidities (sinusitis, nasal polyps, aspirin intolerance, obesity and GORD). Exhaled nitric oxide was higher in patient with exacerbations (despite the limited number of data), and were more frequently treated with high dose ICS, OCS and tiotropium.

From the whole sample, we selected patients with relevant comorbidities (rhinosinusitis, nasal polyps, GOR, obesity, etc) from patient without relevant comorbidities. When we checked for the

Table 3
Comparison between patients divided according to the level of asthma control (according to GINA).

	Poorly controlled ($N = 75$)	Partially controlled ($N = 144$)	Well controlled($N = 77$)
General characteristics			
Age, yrs	53.4 ± 13.5	53.6 ± 13.7	47.5 ± 13.4$^{\S 1}$
Gender, M/F %	34.7/65.3	38.9/61.1	36.4/63.6
Smoke, Y/Ex/N %	4.0/25.3/70.7	4.2/28.5/67.4	2.6/27.3/67.5
PY (ex and actual smokers)	15 (1.5–67.5)	10 (0.5–57)	10 (1–30)
BMI	27 (18.3–40.7)	26.7 (17.3–46.8)	25.7 (16.7–39.1)*
Familiarity for asthma, *n*(%)	31 (44.9)	61 (43.3)	34 (44.7)
Onset of asthma, yrs	29.5 (0–68)	29 (0–75)	20 (0–65)§
Total serum IgE, UI/ml	312 (42–2000)	376 (27–2353)	326.7 (26–1145)
Comorbidities			
Rhinitis, *n* (%)	51 (68.9)	93 (65)	49 (65.3)
Sinusitis, *n* (%)	28 (38.4)	49 (35.5)	21 (28.4)
Nasal polyps, *n* (%)	20 (27.8)	34 (24.1)	17 (22.7)
Aspirin intolerance, *n* (%)	24 (33.8)	26 (19.1)	13 (17.6)§
Obesity, *n* (%)	25 (33.3)	34 (23.6)	9 (11.8)*
GORD, *n* (%)	35 (47.3)	51 (37)	18 (24.3)*
Mental disorders, *n* (%)	8 (11.3)	14 (10.1)	1 (1.4)§
Lung function			
Pre-BD FEV1, Lt	1.77 ± 0.72	2.02 ± 0.71	2.51 ± 0.86$^{\#1}$
Pre-BD FEV1, % of pred.	64.1 ± 19.8	72.8 ± 18.5	88.7 ± 17.6$^{\#}$
Post-BD FEV1, % of pred.	70.9 ± 19.9	77.2 ± 20.5	87.8 ± 15.4$^{\#2}$
Inflammatory markers			
FeNO, ppb	28.4 (4.8–246.6)	24 (0–81.3)	22.4(0–117)
Blood eosinophils,. n/mm^3	266.8 (0–1370)	300 (0–1570)	260 (10–1122)
Blood eosinophils, %	3.7 (0–22.5)	4.3 (0–13.4)	3.6 (0–17)
ACT score	17 (6–22)	21(14–25)	24(16–25)$^{\#}$
Therapy			
High dose of ICS, %	48.0	47.9	31.2§
LABA, %	89.3	95.7	81.6$^{\#}$
OCS, %	12.1	9.6	1.4§
Tiotropium, %	22.5	11.9	6.9*
Antileukotrienes, %	61.4	63.7	50
Theophylline, %	16.9	9.2	8.5
Months of Omalizumab therapy	29.5 (4–96)	32 (5–95)	36 (4–120)

$^{\S}p < 0.05$; $^{*}p < 0.01$; $^{\#}p < 0.001$; $^{\S 1}$ = test post hoc not significant between poorly and partially controlled; $^{\#1}$ = test post hoc not significant between poorly and partially controlled; $^{\#2}$ = test post hoc not significant between poorly and partially controlled.
PY = packs year; BMI = body mass index; GORD = gastro-oesophageal reflux disease; BD = bronchodilator; FEV1 = forced expiratory volume in the 1st second; FeNO = fractional exhaled nitric oxide; ACT = asthma control test; ICS = inhaled corticosteroids; LABA = long-acting β2-agonists; OCS = oral corticosteroids.

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Table 4
Comparison between patients divided according to the presence of te number of exacerbations in the last year of omalizumab treatment.

	No exacerbations ($N = 167$)	Exacerbations≥1 ($N = 125$)
General characteristics		
Age, yrs	51.6 ± 13.2	52.5 ± 14.4
Gender, M/F %	39.5/60.5	34.4/65.6
Smoke, Y/Ex/N %	3.6/28.1/67.1	3.2/25.6/71.2
PY (ex + current smokers)	12.5 (0.5–57)	10 (1.2–67.5)
BMI	26.0 (16.7–40.6)	27 (17.4–46.8)[§]
Familiarity for asthma, *n*(%)	72 (45.3)	52 (42.3)
Onset of asthma, yrs	24.5 (0–71)	29 (0–75)
Total serum IgE, UI/ml	363 (26–2353)	303 (31–2000)
Comorbidities		
Rhinitis, *n* (%)	108 (65.9)	80 (64.5)
Sinusitis, *n* (%)	43 (27)	52 (43.3)*
Nasal polyps, *n* (%)	30 (18.5)	43 (35.2)*
Aspirin intolerance, *n* (%)	25 (15)	35(29.4)*
Obesity, *n* (%)	28 (16.9)	38 (30.4)*
GORD, *n* (%)	47 (29.4)	55(45.1)*
Mental disorders, *n* (%)	10 (6.3)	11 (9.2)
Lung function		
Pre-BD FEV1, L	2.19 ± 0.83	1.93 ± 0.74*
Pre-BD FEV1, % of pred.	77.8 ± 18.6	70.6 ± 22.4*
Post-BD FEV1, % of pred.	81.6 ± 16,3	73.0 ± 23.6*
Inflammatory markers		
FeNO, ppb	22 (3.70–246.6)	27 (0–239.1)[§]
Blood eosinophils, *n*/mm3	260 (10–1266)	316.9 (0–1570)
Blood eosinophils, %	3.9 (0–17)	4.3 (0–22.5)
ACT score	22 (10–25)	20 (6–25)[#]
Therapy		
High dose of ICS, %	37.1	53.6*
LABA, %	89.7	91.1
OCS, %	3.3	12.5*
Tiotropium, %	7.0	21.4[#]
Antileukotrienes, %	57.9	59.8
Theophylline, %	9.1	11.7
Months of Omalizumab therapy	32 (5–79)	36 (4–120)

PY = packs year; BMI = body mass index; GER = gastro-oesophageal reflux; BD = bronchodilator; FEV1 = forced expiratory volume in the 1st second; FeNO = fractional exhaled nitric oxide; ACT = asthma control test; ICS = inhaled corticosteroids; LABA = long-acting β2-agonists; OCS = oral corticosteroids.
[§]$p < 0.05$; *$p < 0.01$; [#]$p < 0.001$.

distribution of asthma control in these two different groups, we found that uncontrolled patients were more often represented in the group with comorbidities (Fig. 2). When only patients without comorbidities were considered, the level of control was not associated with any particular asthma feature, except, as expected, with pulmonary function which was poorer in uncontrolled patients (data not shown).

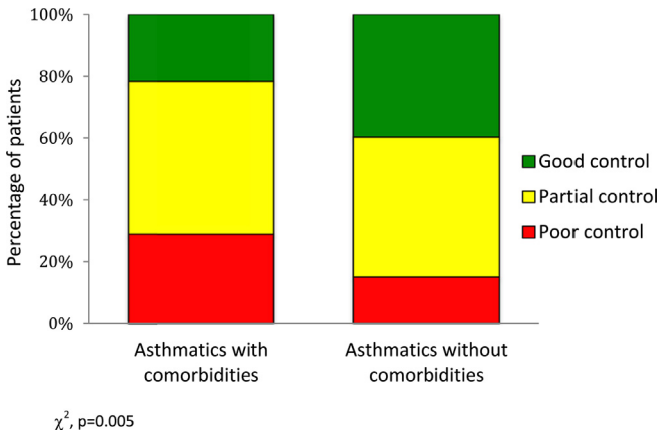

Fig. 2. Asthma control in patients divided according the presence of comorbidities.

Finally, we performed a multivariate analysis, taking as dependent variables the level of asthma control (ACT > or < 20) or the presence of at least one exacerbation in the last year of omalizumab treatment, and as independent variables several clinical findings (age, gender, smoking habit, comorbidities, and duration of omalizumab treatment). We observed that only aspirin intolerance (OR: 2.379, IC: 1.207–4.688) and obesity (OR: 2.446, IC: 1.264–4.736) significantly explained the asthma control according to ACT, while post-bronchodilator FEV1 < 80% (OR: 1.948, IC:1.01–3.795) and obesity (OR: 2.224, IC: 1.015–4.872) significantly explained the presence of one or more exacerbations in the last year of omalizumab treatment.

4. Discussion

This cross-sectional observational study included a large number of patients treated for a mean of 3 years with omalizumab. **They represent a significant sample of the whole group of Italian patients treated with omalizumab, because patients treated with omalizumab are currently 2400 about in Italy (data from the vendor).** The general characteristics of these patients correspond to those expected according to the indication for the use of omalizumab: middle age, predominantly female, with long-lasting history of asthma, allergic sensitivity to perennial allergens (mainly house dust mites) and several comorbidities.

The main aim of this study was to assess the level of asthma control (accurately derived from the assessment of all clinical and functional data included in the evaluation of asthma control according to GINA) in this group of patients treated for a long period with omalizumab. In our study, only 25% of such patients were not controlled despite treatment with omalizumab; this was partially confirmed by the ACT score, which showed values lower than 20 in one third of the patients. Also FEV1 measurements (both before and after bronchodilator) confirmed the mild impairment of pulmonary function, with the presence of an FEV1 post-bronc < 80% in a relevant proportion of the patients. Markers of airway inflammation, although available in a part of the patients, confirmed the partial control of the disease. These results are original, because to our knowledge no study has evaluated in details the level of asthma control according to GINA in a large sample of patients treated for a long period with omalizumab. Considering that, according to the indications for the prescription of omalizumab in Italy, patients at enrollment should be not controlled, this means that a positive effect of the omalizumab treatment may persist for years in the large majority of these patients.

The positive effect of the treatment was also confirmed by the high rate of reduction in asthma exacerbations, and by the significant reduction in emergency room accesses or hospitalization for asthma, when data before and after omalizumab treatment were compared. This is in agreement with many other studies performed in different countries [8–17]. **The impact on the number and severity of asthma exacerbations, as demonstrated in the registrative studies [5], is probably the major effect of the omalizumab treatment. Considering that a high rate of exacerbations, as experimented by these patients in the pre-omalizumab period, is responsible for a poor quality of life [22], the significant reduction in these events may be the major determinant of the improvement in the quality of life observed in these severe asthmatics**.

This is one of the few studies using the measurement of exhaled nitric oxide in a large number of patients after long-term treatment with omalizumab. Apart from some studies where few patients from single centre studies were assessed, few studies included measurements of airway inflammation on a large number of patients [23]. In our study, almost 50% of the patients had a higher

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than normal blood eosinophil count and/or exhaled nitric oxide concentration during omalizumab treatment. Although only a minority of these patients had high levels of these biomarkers (blood eosinophils > 500 cells/ul in 21.5%, and exhaled nitric oxide > 50 ppb in 19.8%), the persistence of an even mild inflammation suggests that the inflammatory process at the basis of asthma symptoms was not completely controlled. The discrepancy between increased biomarkers of airway inflammation and clinical asthma control has been frequently reported in the literature [24], and the correlation between Asthma Control Test and biomarkers is poor [25]. Increased biomarkers of airway inflammation in stable controlled asthma have been considered as a potential future risk (in terms of recurrence of asthma symptoms when ICS were reduced, future asthma exacerbations in the presence of specific triggers, or progressive decline in FEV1) [26]. If these biomarkers may be used for the decision on continuing, reducing or stopping therapy with omalizumab is not known.

The main determinants of the lack of control in these patients were related to the presence of several comorbidities, which were more frequently represented in not controlled patients compared to well controlled or partly controlled patients. This observation was expected, because the relevant burden that upper airway disease, obesity, GORD, smoking habit, and psychiatric disorders may cause on asthma symptoms, pulmonary function and response to treatment, and therefore on asthma control, is well known [2,27]. We can speculate that comorbidities, although appropriately treated, may represent clinical conditions on which omalizumab is partially or not effective, thus explaining the poor asthma control reached by these patients. Although we do not have specific data on the level of asthma control in this subgroup of patients before omalizumab treatment, we might speculate that in this specific subgroup the cost-effectiveness of omalizumab treatment should be accurately evaluated.

As regards the type of allergic sensitization, we did not find any relationship between the level of asthma control and the sensitivity to specific allergens (such as moulds) which are believed to be associated with more difficult asthma [28].

In summary, **as our study aimed to assess the level of control in severe asthmatic under omalizumab treatment**, this study shows that a large percentage of these patients treated for a long period of time with omalizumab reached an acceptably good asthma control. Comorbidities are the main responsible of the lack of asthma control. These informations might be useful in the decisional strategy of omalizumab treatment, and in the assessment of the "best patient" where omalizumab treatment is strongly recommended.

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Table 5
Clinical characteristics of the 10 patients in whom a level of asthma control (according to GINA) was not available

General characteristics	
Number of subjects	10
Age, years	53.4 ± 12.7
Gender, M/F %	30/70
Smoke, Yes/Ex/No %	0/20/80
PY (ex + current smokers)	0 (0–4)
BMI	24.6 (17.4–40)
Familiarity for asthma, *n*(%)	8 (80)
Age of onset, years	34 (0–49)
Total serum IgE, UI/ml	347.5 (54–694)
Comorbidities	
Rhinitis, *n* (%)	7 (70)
Sinusitis, *n* (%)	2 (20)
Nasal polyps, *n* (%)	6 (60)
Aspirine intolerance, *n* (%)	1 (10)
Obesity, *n* (%)	1 (10)
GORD, *n* (%)	1 (10)
Mental disorders, *n* (%)	1 (10)
Sensitization to allergens	
House dust mites, *n* (%)	6 (60)
Dog, *n* (%)	0 (0)
Cat, *n* (%)	2 (20)
Moulds, *n* (%)	3 (3)
Parietaria pollen, *n* (%)	2 (20)
Grass pollen, *n* (%)	2 (20)
Pollen from trees, *n* (%)	2 (20)
Polyallergics, *n* (%)	3 (30)
Lung function	
Pre-BD FEV1, L	2.04 ± 0.58
Pre-BD FEV1, % of pred.	65.8 ± 11.3
Post-BD FEV1, L	2.06 ± 0.45
-BD FEV1, % of pred.	77.6 ± 16.5
Inflammatory markers	
FeNO ($n = 4$), ppb	26.5 (14–52)
FeNO>25 ppb, *n* (%)	2 (50)
Blood eosinophils, *n*/mm3	205.9 (5.3–1292)
Blood eosinophils, %	4.1 (2.2–9.7)
ACT score	20.5 (18–25)
ACT score ≥20, *n* (%)	7 (70)

Data are reported as mean ± SD, or median and range.
PY = packs year; BMI = body mass index; GERD = gastroesophageal reflux disease. BD = bronchodilator; FEV1 = forced expiratory volume in the 1st second; FeNO = fractional exhaled nitric oxide.
ACT = asthma control test.

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