



Omalizumab management beyond clinical trials: The added value of a network model



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ABSTRACT

Background: Omalizumab is effective and safe in severe allergic asthma. Few data are available about its impact on lung function and on asthma comorbidities, long-term follow-up of treated patients, adherence, non-responders profile, and optimal treatment duration.

Objective: We aimed at evaluating omalizumab-related clinical outcomes and unmet needs in a real-life setting.

Methods: We created a collaborative network (NEONet – North East Omalizumab Network) involving 9 Allergy and Respiratory referral centres for severe asthma placed in the North-East of Italy. Patients' data were entered into a common study database shared by all the participating physicians. A preliminary retrospective analysis was performed.

Results: Patients come from a common well-defined geographical and environmental district providing a homogeneous population sample. A moderate but statistically significant improvement of the FEV₁, and an increasing proportion of exacerbations-free patients were observed since the treatment start. These findings were independent of the baseline severity of bronchial obstruction. A positive impact of omalizumab on rhinitis in patients with both asthma and rhinitis was detected. Moreover the efficacy of omalizumab on asthma seemed not to be affected by the baseline severity of rhinitis.

Conclusion: Our retrospective analysis represents a preliminary report from the NEONet activity. It confirmed omalizumab efficacy and provided some new insights about its impact on lung function and on comorbid rhinitis. The network approach, under a prospective view, allows creating a large uniform database, by means of a standardized shared tool for data collecting, and joining a multidisciplinary expertise.

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1. Introduction

Omalizumab is a humanized recombinant anti-IgE monoclonal antibody used as a treatment option in patients with severe allergic asthma (Global Initiative for Asthma – GINA – step 5 therapy) [1]. Its efficacy and safety as an add-on therapy has been proved in several controlled studies [2–6], showing a significant reduction of yearly exacerbations as well as a steroid-sparing effect and an improvement of quality of life (QoL)-related outcomes. However, in controlled studies patients are selected according to strict criteria, they are regularly assessed during the treatment and their

adherence is rigorously monitored. These conditions are rather different from daily practice. Indeed in this setting the drug is used in a broader range of patients, matching less selective prescription criteria. In fact according to several studies only 4%–6% of treated patients in daily routine meet the criteria to be eligible for clinical controlled trials [7,8]. Therefore the clinical efficacy of any drugs, although proved by controlled studies, has to be confirmed in real life setting. There are published data concerning international real-life experience [9–14] but only limited Italian data evaluating the clinical outcomes achieved in daily clinical practice are to date available [10]. Furthermore few published data concern adherence to the treatment with omalizumab, its impact on lung function and on asthma comorbidities, long-term follow-up and non-responders profile. As biological drugs are used only in few selected cases, every specialist assesses their efficacy and safety usually on a small group of patients. A more reliable evaluation of omalizumab can be achieved on a larger population, by means of the organization of a collaborative network among referral centres. According to this rationale, an Italian Network called NEONet (North East Omalizumab Network) has been recently created. It presently involves 9 Allergy and Respiratory referral centres for severe asthma, all placed in the North-East of Italy. NEONet mainly aims at studying a homogeneous population sample (coming from a well-defined geographical and environmental district) in order to investigate efficacy, safety and tolerability of omalizumab in daily clinical practice, adherence to the treatment, and its impact on lung function and asthma comorbidities over short and long-term follow-up. The retrospective observational multi-centre study here presented is a preliminary report of the NEONet activity.

2. Materials and methods

2.1. Study population

This retrospective non-interventional observational multi-centre study included consenting patients of both genders, older than eighteen years, treated by the NEONet referral centres (outpatient asthma clinics at University Hospitals and General Hospitals), who had received at least one dose of omalizumab at the time of observation. The criteria for correct selections of patients eligible to receive Omalizumab treatment were set as part of the study. The criteria established by the regulatory Italian Agency AIFA (Agenzia Italiana del Farmaco) are the following: i) severe asthma (level 5 of GINA classification) [1]; ii) total serum IgE between 30 and 1500 IU/ml; iii) evidence of sensitization to at least one perennial allergen (detected by prick test or serum specific IgE); iv) poor control of asthmatic disease (FEV₁ less than 80% of normal value, exacerbations responsible for unscheduled visits and/or emergency room visits and/or hospitalizations for asthma during the previous year), despite ongoing pharmacological treatment according to proper GINA therapy step [1], correctly taken by the patient; v) exclusion of respiratory diseases that may share common clinical manifestations with severe asthma (i.e. acute bronchopulmonary aspergillosis, vasculitis). Since it was a retrospective observational study aimed at evaluating all the patients who received the drug as part of routine clinical practice, the prescription without full accordance with AIFA requirements was not considered as exclusion criteria. In particular subjects without evidence of sensitization to at least one perennial allergen were included as well.

2.2. Data collection

Anonymized-coded data were collected from paper and electronic hospital medical records between April and September 2013

and were entered into a study database by participating physicians. The data of all patients who had received at least one dose of Omalizumab were analysed. The treatment duration was calculated and its impact on the efficacy clinical outcomes (lung function and exacerbations) was evaluated.

For each patient the following parameters before the treatment and at the time of evaluation were investigated: lung function (FEV₁, FVC); rate of exacerbations (major exacerbation: need for Emergency Department visits or hospitalization; minor exacerbations: need for oral steroids); upper respiratory comorbidities (allergic rhinitis and nasal polyposis). Allergic rhinitis was assessed according to ARIA classification of severity [15]. Head TC and/or rhinoscopy were performed for nasal polyps evaluation. The impact of the upper airway comorbidities and their severity on the efficacy clinical outcomes (lung function and exacerbations) was considered.

A global evaluation of efficacy was based upon responses to the GETE Questionnaire [16], completed by the physicians for every patient. GETE is a five-point scale, where 1 = excellent (complete control of asthma), 2 = good (marked improvement), 3 = moderate (discernible, but limited improvement), 4 = poor (no appreciable change) and 5 = worsening. The rating of symptoms control as 'excellent'/'good', 'moderate' or 'poor' allowed the patient to be respectively defined as 'responder', 'low responder' or 'not responder'. The evaluation was performed at the time of the interim-evaluation. Details of any adverse event occurring during Omalizumab treatment were also recorded. Adherence to the treatment was assessed; for each patient the number of missing scheduled appointments for administration since the treatment start was calculated.

2.3. Statistical analysis

For continuous variables mean and standard deviation are reported. For discrete variables number of subjects and percentages are reported. To investigate statistical relevance, Student's *t*-test and Paired Student's *t*-test were used for continuous normally distributed variables, Mc Nemar test was used for dichotomic paired variables, and χ^2 test for categorical data. For all the analysis, IBM SPSS Statistics for Windows, Version 20.0, was used.

To investigate the possible relation of upper airway comorbidities with the efficacy clinical outcomes (lung function and exacerbations) linear regression models (lung function) and binary logistic regression models (presence of exacerbations) were applied.

3. Results

Data of all 59 patients included in the study were analysed. In the population study a slight prevalence of females was observed (males 49.2%; females 50.8%). Mean age was 45.59 years (SD: 11.51). All the patients were allergic to common perennial aeroallergens, mostly house dust mite (84.8%). A sensitization to local pollens (grass, birch, parietaria) was detected in 33 patients (55.9%), being grass pollens the most frequent seasonal allergen (81.8%). Multiple sensitizations were recorded in 67.8% of patients. Among polysensitized patients, the most common sensitization profile included house dust mites and grass pollen (44.1% of patients). Total IgE serum levels did not significantly differ between males (mean: 516.7; St Dev: 556.20) and females (mean: 398.6; St Dev: 318.96) ($p = 0.319$). The mean length of the disease was 18.2 years (St Dev: 15.4). As far as smoke habit, 67.8% had never smoked, 30.5% were former-smoker and 1.7% current smoker. Baseline data concerning study population are shown in Table 1.

Patients were treated with a mean dose of 322.9 mg (SD: 133.77; range: 150 mg–600 mg), all patients receiving a dosage within the recommended range. According to AIFA suggested schedule, 34

Table 1
Baseline characteristics of study population.

Total population – <i>n</i>	59
Age, years – mean (SD)	45.59 (11.51)
Sex, M/F – <i>n</i> (%)	29/30 (49.2/50.8)
Weight, kg – mean (SD)	Males: 77.73 (16.96); Females: 63.55 (11.46)
Total IgE, IU/ml – mean (SD)	456.7 (451.40)
Duration of allergic asthma, years – mean (SD)	18.2 (15.40)
Smoking history – <i>n</i> (%)	
Never smoked	40 (67.8)
Ex smoker	18 (30.5)
Current smoker	1 (1.7)
Positive skin prick test and/or sIgE – <i>n</i> (%)	
Mites	50 (84.8)
Cat	15 (25.4)
Dog	10 (17.0)
Alternaria	4 (6.8)
Aspergillus	7 (11.9)
Grass	27 (45.8)
Birch	9 (15.2)
Parietaria	6 (10.2)
Olea	3 (5.1)
Single sensitization	19 (32.2)
Multiple sensitizations	40 (67.8)
Basal lung function parameters – mean (SD)	
FEV ₁	2.02 (0.65)
FEV ₁ %	63.78 (13.49)
FVC	3.14 (0.90)
FVC%	81.81 (13.68)
FEV ₁ /FVC	65.2% (13.10)

n = number of subjects. SD = standard deviation. sIgE = serum specific IgE.

patients were treated with a monthly injection schedule, whereas the remaining 25 received only one injection every two weeks. The mean treatment duration was 22.97 months (SD: 16.55). According to the linear regression model the correlation between the clinical outcomes reported below and the treatment duration is not statistically significant ($p > 0.05$).

3.1. Clinical outcomes

3.1.1. Lung function

A significant improvement of FEV₁ (mean absolute value and % of predicted) was observed after treatment in the whole group of patients (Fig. 1), with no significant difference between males and females and between smokers (current and former) and non-smokers (Fig. 2).

FEV₁ value significantly correlated with FEV₁ recorded at the time of evaluation but not with the treatment duration ($p = 0.072$). Moreover, in accordance with the FEV₁ cut off suggested by GINA

recommendations for severe persistent asthma [1], we separately compared the FEV₁ improvement in two groups, the first with FEV₁ > 60% at baseline, the latter equal to or below this value. Both the two groups shared a significant functional improvement in terms of absolute value and % of predicted, without statistical significance between them (Fig. 3). The linear regression model confirmed the absence of significant correlation between the FEV₁ value at baseline and at interim evaluation ($p = 0.108$). A significant improvement of FVC was also detected in the whole group ($p < 0.001$), with no significant difference between males and females.

3.1.2. Exacerbations

Considering both major and minor exacerbations, the proportion of event-free patients at “interim” evaluation was significantly higher compared with the proportion of event-free patients before the treatment start (Fig. 4).

The major exacerbations reduction did not significantly differ between the patients with basal FEV₁ over or below 60% of predicted ($p = 0.179$). Similarly no significant difference between these two groups was detected regarding the use of oral steroids (considered as a marker of minor exacerbations) ($p = 0.354$). The exacerbation reduction did not significantly differ was between smokers (current and former) and non-smokers (Fig. 5).

3.1.3. Upper respiratory comorbidities

Before the omalizumab treatment 82% suffered from allergic rhinitis and after treatment 4% recovered completely. In the remaining 78% a trend towards less severe symptoms, according to the ARIA classification, was recorded (Fig. 6). Moreover the lung function improvement was similar in patients without rhinitis or affected by mild rhinitis and in patients with moderate to severe allergic rhinitis and/or nasal polyps (Fig. 7). The linear regression model confirmed that the clinical efficacy of omalizumab in terms of lung function improvement ($p = 0.442$) and exacerbations ($p = 0.618$) seemed to be independent from the presence and the severity of upper respiratory comorbidities.

3.1.4. Safety and tolerability

No systemic reactions were registered. Eight patients (13.4%) complained of a large local reaction that occurred at the site of injection few minutes after the first administration of omalizumab. Symptoms recovered about 30 min after the administration of an oral anti-H1. No other adverse events occurred. No treatment discontinuations were registered because of local or systemic adverse events.

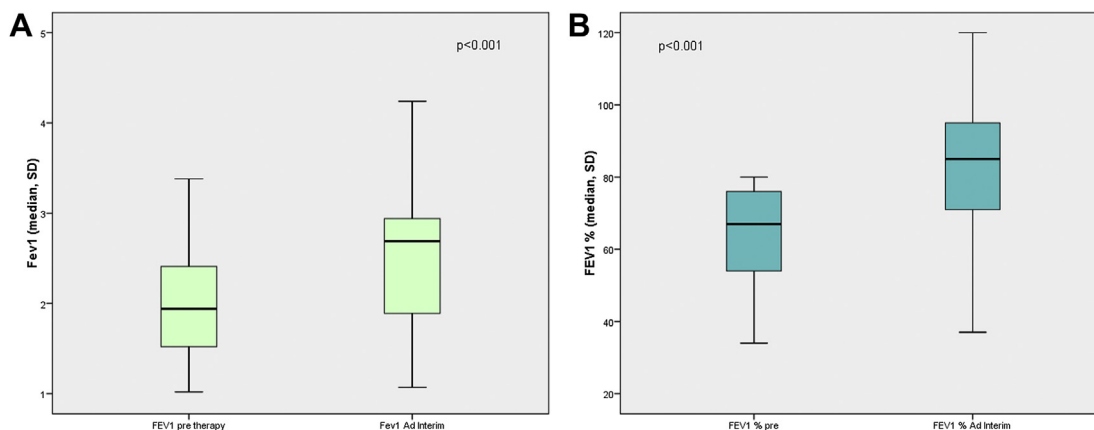


Fig. 1. FEV₁ value (L) at baseline (pre) and at the time of analysis (ad interim).

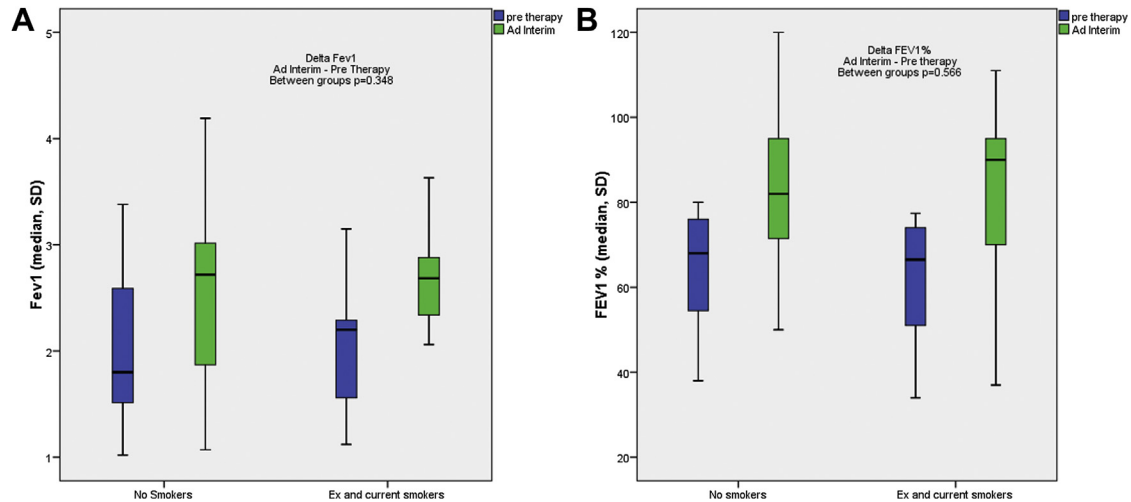


Fig. 2. FEV₁ value (L) at baseline (pre) and at the time of analysis (ad interim) in smokers (current and former) and in non-smokers.

3.1.5. GETE

In accordance to the rating performed through the GETE assessment, 77.4% of treated patients showed complete control of asthma or marked improvement and were considered as “responders”. In 17.0% of patients the improvement was rated as discernible, but limited and they were classified as “low responders”. In 5.7% no appreciable change was recorded and they were described as “not responders”. None of the patients showed asthma worsening.

3.1.6. Adherence and treatment discontinuation

Adherence to treatment was high; no missing scheduled appointments for administration were registered. The dropout rate was 13.4% (8 patients). Two patients discontinued the treatment for pregnancy; three patients stopped the treatment after 6, 12 and 24 months respectively for inefficacy (based upon lack of lung function improvement/exacerbation rate decrease); two patients for achieving of complete asthma control with GINA step 2 therapy; one patient for migration in another country. None of the dropout cases was due to treatment-related adverse effects.

4. Discussion

The clinical efficacy of omalizumab for the treatment of patients affected by severe allergic asthma is sustained by several data coming

from both clinical trials and real-life experiences [2–6,9–14]. Our retrospective analysis, that represents a preliminary report of the NEONet activity, confirms that the most impressive clinical effect concerns the reduction of major and minor exacerbations. Few published studies have included lung function assessment as a primary outcome. We observed a moderate but statistically significant improvement of the FEV₁, independently of the treatment duration and of the smoking habits. Of note the low number of current and former smokers may affect the strength of this result from a statistical point of view. It is remarkable that the impact of baseline lung function features on clinical outcomes seems to be negligible, as both patients with moderate (FEV₁ > 60%) and severe (FEV₁ ≤ 60%) baseline bronchial obstruction achieved a significant reduction of exacerbations and a significant lung function improvement as well. To our knowledge no other studies have focused specifically on this aspect and further evaluations are needed. However our findings agree with the multi-step anti-inflammatory action of omalizumab, demonstrated by in vitro and in vivo models [17,18], and recently proved to overturn the remodelling in a small number of patients after a long-term treatment [19]. The current discrepancy between a more relevant clinical effect and a less significant impact on lung function could be related to the need of more prolonged treatment to improve lung function [13]. As far as inflammation assessment, biomarker data (exhaled NO, sputum, peripheral blood eosinophils)

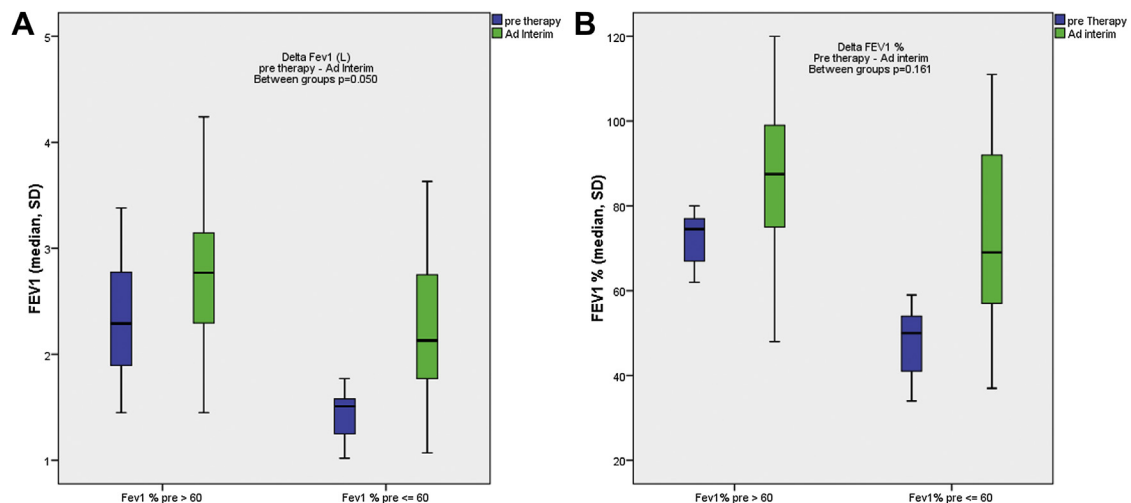


Fig. 3. FEV₁ value (L) at baseline (pre) and at the time of analysis (ad interim) in subgroups of patients with different baseline bronchial obstruction severity.

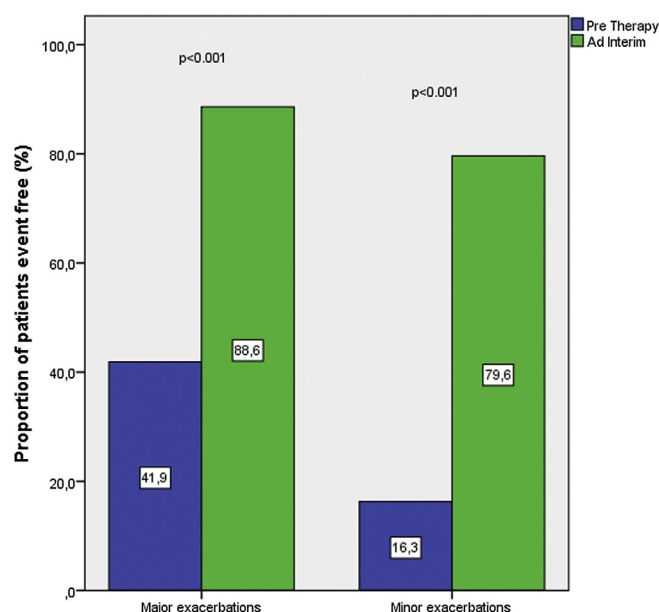


Fig. 4. Proportion of exacerbations-free patients before (pre therapy) and after treatment start (ad interim).

were not available in all patients enrolled in our survey. It certainly represents a limitation to the study. It should be noted that the high doses of inhaled and oral corticosteroid treatment that patients with severe asthma commonly need may affect the available markers of Th2-driven inflammation and their correlation with clinical response to omalizumab.

Rhinitis is the most common asthma comorbidity and a risk factor for difficult asthma control [15]. Some clinical trials have demonstrated the efficacy of omalizumab in treating allergic rhinitis and nasal polyps [20,21]. Nevertheless a specific real-life evaluation of the impact of omalizumab treatment on asthma and rhinitis in patients with both the diseases lacks. According to ARIA classification [15], in our population the proportion of patients affected by moderate to severe rhinitis at baseline is significantly higher at

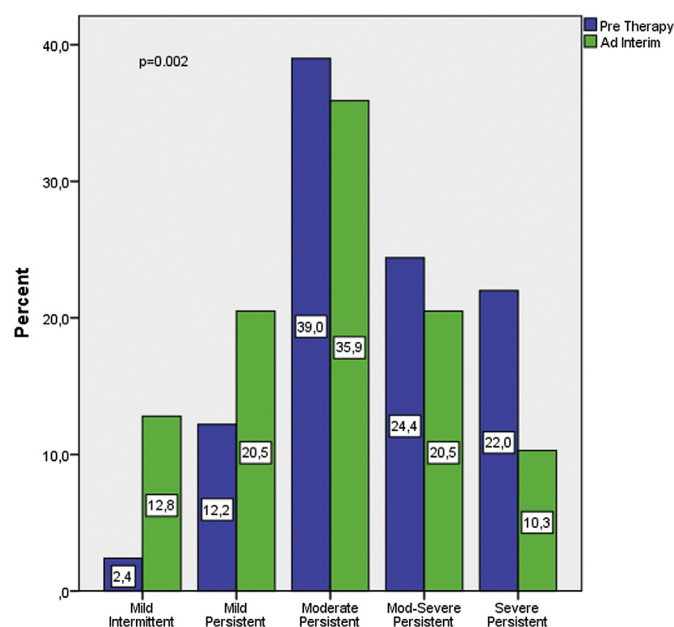


Fig. 6. ARIA classification of rhinitis severity at baseline (pre-therapy) and at the time of analysis (ad interim). Percent = percentage of patients.

baseline then at the time of our evaluation, while an opposite trend is shown for mild rhinitis. This observation needs to be confirmed, however it suggests a positive impact of omalizumab also on rhinitis in patients with both asthma and rhinitis. Moreover it is remarkable that the improvement of clinical outcomes is not significantly different in patients with or without moderate to severe rhinitis at baseline. It suggests that the efficacy of omalizumab on asthma is not affected by the baseline severity of nasal disease. It is much more important if we consider that nasal comorbidities are normally responsible for an increased asthma exacerbations rate [15].

As far as safety, no systemic reactions were registered in our population. Eight patients (13.4%) complained of a self-limiting local reaction that occurred at the site of injection few minutes after the first administration. It wasn't bothersome as all patients continued the treatment. In fact in our population no treatment discontinuations were registered because of local or systemic treatment-related adverse events. In literature systemic reactions

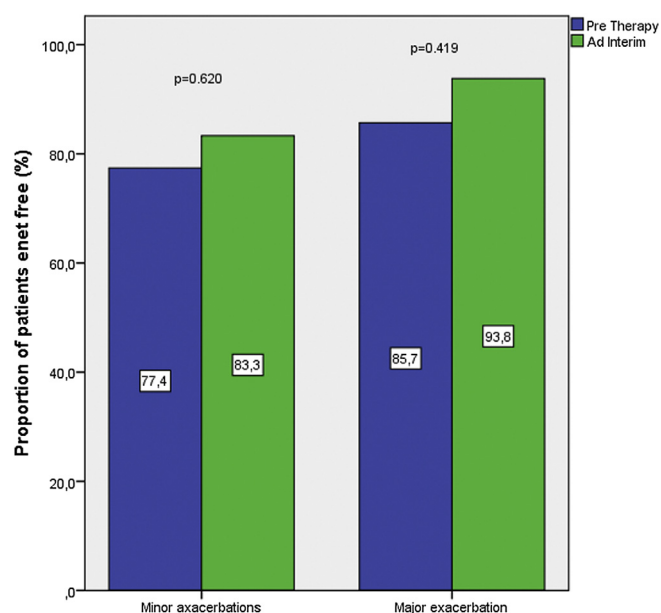


Fig. 5. Proportion of exacerbations-free patients after treatment start (ad interim) among smokers (current and former) and non-smokers.

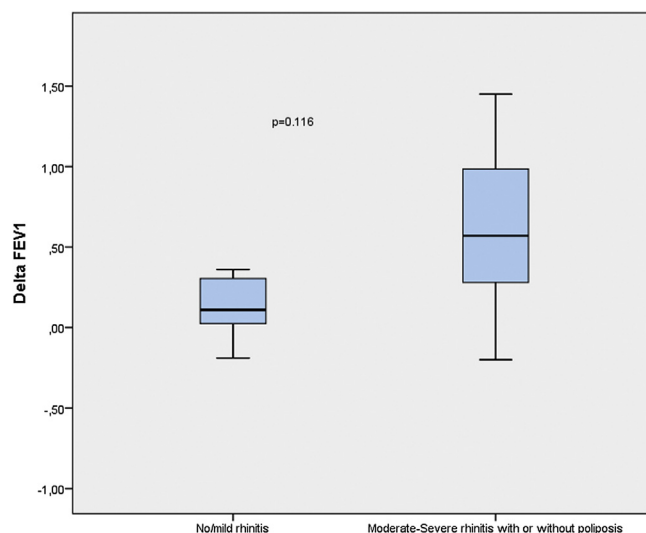


Fig. 7. FEV₁ value (L) at baseline and at the time of analysis in subgroups of patients with different baseline rhinitis severity.

have been seldom reported [22,23], and no specific risk factors have been defined. It should be noted that data about long term safety and tolerability profile are lacking, as to our knowledge it that was assessed up to 4 years in one study [24]. It is thus important that after each injection every patient is kept under medical observation and every reaction is recorded and graded.

The overall adherence to treatment was high, as no missing scheduled appointments for administration were registered. As the physician administers the treatment at hospital the adherence rate is expected to be high [25]. On the other hand few published data focus on long-term adherence rate. It is noteworthy that 17.0% and 5.7% of patients have been classified as low and not responders respectively. Three out of 59 patients stopped the treatment for inefficacy. Looking at the published evidences, the mean dropout rate for inefficacy in real life is about 10% [9–14]. It outlines the need for a more accurate patient selection through biomarkers able to better characterize the “responder/not responder” patients beside the available criteria.

A major strength of our work is that the treated patients come from the same, well-defined geographical district and they share very similar environmental variables, such as pollution, pollen load, medical practice and cultural customs. As all these factors can act as environmental confounding factors that affect the clinical outcome of the treatment, a homogeneous population sample is certainly a good background in order to evaluate omalizumab-related clinical outcomes in a real-life setting. By means of the organization of a collaborative network among referral centres, a more reliable evaluation of omalizumab can be achieved on a larger population, as biological drugs are used only in few selected cases, and every single specialist has usually the opportunity to assess their efficacy and safety on small groups of patients. Moreover, our network shares common and easy tools for data collecting (web-platform). It allows, under a prospective view, creating a large uniform database and joining a multidisciplinary expertise, as NEONet involves both allergists and lung specialists. Some limitations have to be outlined. As our collaborative initiative is an ongoing project, the present preliminary retrospective analysis involves a small population sample. Moreover it does not include data about quality of life of treated patients, since no information had been uniformly collected until now. Other studies have proved a positive impact of omalizumab on quality of life [13,14]. Patient Reported Outcomes have been included among the outcomes of our prospective surveillance.

5. Conclusions

In conclusion, our work confirms efficacy and safety of omalizumab for the treatment of allergic asthma. It provides some new insight concerning: i) the impact of omalizumab on lung function and on nasal comorbidities; ii) omalizumab efficacy in patients with upper airways comorbidities. Further investigations are needed, in order to increase omalizumab effectiveness beyond its efficacy. They should in particular focus on: identification of “responders” profile, optimal treatment duration, impact on comorbidities, long-term safety and tolerability with potential risk factors identification, long-term dropout analysis. These unmet needs represent the “agenda” of our collaborative network.

Conflict of interest/funding sources

The authors have neither conflicts of interest nor funding sources to declare pertaining to this article.

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