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Lung function parameters in omalizumab responder patients: an interesting tool?

Short Title: Lung function and omalizumab

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Authors' contributions

F. Paganin has been involved in the study design, in the data collection, in drafting the article and has given final approval of the version to be published.

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ABSTRACT (249 words)

Background: Omalizumab, an anti-IgE antibody, is used to treat patients with severe allergic asthma. The evolution of lung function parameters over time and the difference between omalizumab responder and non-responder patients remain inconclusive. The objective of this real-life study was to compare the changes in FEV1 of omalizumab responders and non-responders at 6 months.

Methods: A multicenter analysis was performed in 10 secondary and tertiary institutions. Lung function parameters (forced vital capacity (FVC), pre- and post-bronchodilator FEV1, residual volume (RV) and total lung capacity (TLC) were determined at baseline and at 6 months. Omalizumab response was assessed at the 6-month visit. In the omalizumab responder patients, lung function parameters were also obtained at 12, 18 and 24 months.

Results: Mean pre-bronchodilator FEV1 showed improvement in responders at 6 months, while a decrease was observed in non-responders ($+0.2 \pm 0.4\text{L}$ and $-0.1 \pm 0.4\text{L}$ respectively, $p < 0.01$). After an improvement at 6 months, pre- and post-bronchodilator FEV1 remained stable at 12, 18 and 24 months. The FEV1/FVC remained unchanged over time, but the proportion of patients with an FEV1/FVC ratio < 0.7 decreased at 6, 12, 18 and 24 months (55.2%, 54.0%, 54.0% and 44.8%, respectively, $p < 0.05$). Mean RV values decreased at 6 months but increased at 12 months and 24 months ($p < 0.05$). RV/TLC ratio decreased at 6 months and remained unchanged at 24 months.

Conclusion: After omalizumab initiation, FEV1 improved at 6 months in responder patients and then remained stable for 2 years. RV and RV/TLC improved at 6 months.

Key words: asthma, omalizumab, lung function, FEV1

INTRODUCTION (word count: 2675)

Asthma is a heterogeneous disease, defined as a chronic inflammatory airway disorder, which affects about 334 million people worldwide^{1,2}.

Several asthma phenotypes have been identified in cluster analysis studies, and the allergic asthma phenotype is reported to be the most frequent³⁻⁵. Although allergic asthma is usually a mild-to-moderate disease, it can also be severe⁵. Uncontrolled severe asthma is a clinical and economic healthcare burden^{5,6}. Omalizumab, an anti-IgE antibody, is the first approved biotherapy to have been to treat patients with severe allergic asthma^{7,8}. Randomized placebo-controlled trials found that omalizumab significantly decreased the asthma exacerbation rate in severe persistent asthma patients requiring regular inhaled treatment⁹⁻¹¹. Despite extensive research, no predictive marker is currently used, and omalizumab is delivered to an unselected population of patients with severe allergic asthma¹².

Pulmonary function testing, particularly forced expiratory volume in 1 second (FEV1), is widely recommended to diagnose and monitor¹. For the prescription of omalizumab, FEV1 less than 80% is required by the European Medicines Agency⁷. FEV1 is an interesting and reproducible tool to assess the severity and control of asthma¹³. However, it generally provides information about large airway function, and asthma assessment with only FEV1 is somewhat restrictive^{14,15}. Indeed, this parameter does not explore lung inflation or small airways involvement, which are pathophysiological conditions affecting severity and quality of life¹⁶⁻¹⁸.

In clinical trials, little is known about lung function changes after omalizumab initiation. Randomized controlled trials found improved FEV1 in patients receiving omalizumab⁹⁻¹¹. However, in these trials, responders and non-responders were mixed and the studies only lasted 1 year. FEV1 improvement has also been reported in real life studies but results remain inconclusive¹⁹⁻²¹. These studies generally involve a small number of patients. Moreover, there

are no available data about changes in lung function parameters other than FEV1 after omalizumab initiation.

The main objective of the present study was to compare the changes in forced expiratory volume in one second (FEV1) of omalizumab responders and non-responders at 6 months in a real-life study. We also assessed various functional parameters up to 2 years.

MATERIALS & METHODS

Study population

A multicenter retrospective analysis of severe asthma patients treated with omalizumab was performed in 10 secondary and tertiary institutions in France from 2011 to 2014. Inclusion criteria were as follows: 1- Patients over 12 years of age with a diagnosis of severe asthma based on GINA guidelines; 2- uncontrolled asthma despite intensive therapy (*i.e.*, ICS over 1500 µg/d and conventional additive treatment); 3- good compliance to inhaled treatment with self-reported adherence to ICS of over 80%.

Since this was a real-life study, omalizumab indication was at the investigator's discretion. We collected data about The demographics, body mass index (BMI), age of asthma onset, allergen sensitization, diurnal and nocturnal respiratory symptoms, rhinitis, nasal polyposis, gastroesophageal reflux disease (GERD), use of β 2-agonists as "rescue" medication, patients with two or more exacerbation/year, inhaled corticosteroid dosage, oral corticosteroid use and total IgE (kUI/l). French law does not require the approval of an Institutional Review Board or individual patient's consent for such observational, non-interventional and retrospective analyses of medical records. The database was anonymous and complied with the restrictive requirements of the "Commission Nationale de l'Informatique et des Libertés", the organization that ensures the application of data privacy laws in France. Our study was conducted in accordance with legislation.

Procedure

Pulmonary function tests (PFT) were performed following American Thoracic Society/European Respiratory Society guidelines²². Lung function parameters were determined in all patients at baseline and at 6 months. Forced vital capacity (FVC), vital capacity (VC), pre- and post-bronchodilator FEV1, forced expiratory flow between 25% and 75% of FVC (FEF25%-75%), residual volume (RV) and, total lung capacity (TLC) values were expressed as both absolute values (liters or liters/sec) and percentages of predicted values according to gender, height and age²³. Patients were excluded if the 6-month visit was outside the range of 90 to 210 days. Omalizumab response was assessed at the 6-month visit by the physician in charge of each patient, by global evaluation of treatment effectiveness (GETE)¹⁰. In the omalizumab responder patients, lung function parameters were obtained at 12, 18 and 24 months after omalizumab introduction. Omalizumab was maintained at the same dose for all patients over the period of 2 years. A visit is recommended every 3 months in severe asthma patients¹. However, we chose these time points to allow homogeneous presentation in all patients. For non-responder patients, omalizumab was stopped and these patients were removed from the study.

Primary and secondary endpoints

Primary endpoint was the pre-bronchodilator FEV1 difference at 6 months between omalizumab responders and non-responders. Secondary endpoints were post-bronchodilator FEV1, VC, FEV1/FVC, FEF25%-75%, TLC, RV and RV/TLC differences between baseline and 6 months. Data were also collected at 12 months, 18 months and 24 months in omalizumab responders and compared to those assessed at baseline. At 6 months, clinical data and lung function parameters of omalizumab responders and non-responders were also compared to determine potential predictive markers of omalizumab response. Subgroup

analyses of pre-bronchodilator FEV1, post-bronchodilator FEV1, VC, FEV1/FVC, TLC, RV and RV/TLC differences between baseline and 6 months, were conducted for overweight patients (BMI>25 kg/m²), patients taking oral steroids and those with severe obstruction (pre-bronchodilator FEV1<50% of predicted values).

Statistical analysis

Data collection was performed on the capture system software in accordance with ICH3 good clinical practice guidelines. Results were analyzed using SAS software version 9.3. The calculation of the sample size was based on the percentages of omalizumab responders and non-responders (estimated at 75% and 25% respectively) observed in controlled clinical trials⁹⁻¹¹. The sample should comprise 288 patients. The calculation detail is available in the online version. Primary end-point was the comparison of differences in pre-bronchodilator FEV1 between baseline and 6 months in omalizumab responders and non-responders using Student's t-test. Statistical comparisons of lung function parameters in omalizumab responder patients at each time point (baseline, 6, 12, 18, 28 months) were performed using 1-way repeated measures ANOVA. To find a predictive marker of omalizumab efficacy at 6 months, the characteristics that appeared to have a significant impact on the treatment response in the univariate analyses were then fed into a multivariate logistic regression model to identify those which had a significant and independent influence on treatment response. Quantitative data were expressed as mean $\pm$ SD and qualitative data were expressed as percentages (%). The chi-square test was used to compare categorical variables. The means of continuous variables were compared between the 2 groups using Student's t-test. A p value <0.05 was considered to be statistically significant.

RESULTS

A total of 263 asthma patients treated with omalizumab were screened. The flow chart of the study is presented in Figure 1. Among these patients, 51 were out of the time range for the 6-month visit, 2 were under 12 years old, and no details of omalizumab prescription were available in 3 patients. The final analysis was thus conducted on 207 patients.

Baseline patient characteristics

Table 1 summarizes the patients' characteristics at baseline. At 6 months, 46 patients (20.8%, IC 95% [15.3; 26.3]) were considered as non-responders and 164 (79.2%, IC 95% [73.7; 84.8]) as responders to omalizumab. Among responders and non-responders, 86.6% and 95.3% were sensitized to one or more allergens. The difference was not statistically significant.

Baseline lung function parameters are detailed in Table 2. Mean pre-bronchodilator FEV1 absolute values were similar in the two groups ($p=0.40$). By contrast, mean pre-bronchodilator FEV1 expressed as percentage of predicted values was significantly higher in responders than non-responders ($p<0.05$). As a consequence, the percentage of patients with FEV1 below the predicted 50% was significantly higher in non-responders than in responders ($p<0.01$). Similarly, the FEV1/FVC ratio was lower in non-responders ($p<0.05$), but the percentage of patients with FEV1/FVC below 0.7 was not statistically significant ($p=0.07$). Post-bronchodilator FEV1 and all volumes (TLC, RV and TLC/RV) were similar in the two groups. Using multivariate logistic regression analysis, no baseline data were identified as discriminating markers of omalizumab response at 6 months (data not shown).

Lung function parameters at 6 months in omalizumab responders and non-responders

The primary endpoint was achieved; at 6 months, mean pre-bronchodilator FEV1 improved in responders, while a decrease was observed in non-responders ($p<0.01$) (Table 3). Similarly, the mean differences in pre-bronchodilator FEV1 percentages of predicted value decreased in non-responders and increased in responders ($p<0.001$). Moreover, changes in mean post-bronchodilator FEV1 and FEF differed in responders and non-responders ($p<0.01$). Conversely, there were no significant differences in VC, FEV1/FVC, TLC and RV changes between the two groups.

Lung function parameters at baseline, 6, 12 and 24 months in omalizumab responders

Mean pre- and post-bronchodilator FEV1 assessed in both absolute values and percentages improved at 6 months and remained stable at 12 and 24 months (Table 4). The proportion of patients with FEV1 below 50% remained relatively unchanged over time. FVC assessed in percentages of predicted values improved at 6 months and stabilized at 12 and 24 months. The FEV1/FVC was unchanged over time but, interestingly, the proportion of patients with a FEV1/FVC ratio < 0.7 decreased over time ($p<0.05$). The FEF profile was similar to that of FEV1 with an increase at 6 months and stabilization at 12 and 24 months. TLC values and percentages of predicted values did not change during the follow-up. Mean RV values decreased at 6 months but increased at 12 months and 24 months ($p<0.05$). RV/TLC ratio decreased at 6 months and remained unchanged at 24 months.

Lung function parameters in subgroups of omalizumab responders at 12 and 24 months

The difference in pre-bronchodilator FEV1 between baseline and the 6-month visit was significantly lower in overweight than in normal weight patients ($p<0.05$) (Supplemental Table 1). FEV1/VC improved from baseline to 6-month visit in normal weight patients but remained unchanged in overweight patients ($p<0.01$). FEF25%-75% improved in both groups at 6 months, but the difference

between baseline and 6 months was greater in normal weight patients ($p<0.05$). The differences in TLC and RV were similar in overweight and non-overweight patients. Patients who were and were not taking oral steroids had a similar profile of changes in lung function parameters between baseline and 6-month visit (Supplemental Table 2). Patients with $FEV1 >50\%$ and those with $FEV1 \leq 50\%$ also had a similar profile, excluding RV values (Supplemental Table 3). The decrease in RV values was 0.1 ± 0.6 and 0.5 ± 0.9 L, respectively, but the difference did not reach statistical significance ($p=0.06$). However, RV change in percentage of predicted value was significantly greater in patients with $FEV1 \leq 50\%$ than in those with $FEV1 >50\%$ ($p<0.05$). RV/TLC decrease was also statistically different between patients with $FEV1 \leq 50\%$ and those with $FEV1 >50\%$ ($p<0.05$).

DISCUSSION

In the present real-life study, we demonstrated that pre-bronchodilator FEV1 change at 6 months was significantly better in omalizumab responders than non-responders. Changes in post-bronchodilator FEV1 and FEF25%-75% were also better, but not those of TLC and RV. After 6 months, pre- and post-bronchodilator FEV1 and FEF25%-75% remained stable over a period of 2 years.

In randomized placebo-controlled trials, significant FEV1 improvements have been reported in asthma patients treated with omalizumab^{9,11}. Busse *et al.* found a mean FEV1 increase from 68.2% at baseline to 72.5% of predicted value at 6 months in the omalizumab group, and from 67.7% to 69.1% of predicted value in the placebo group¹¹. The difference between groups was statistically significant. In the trial carried out by Humbert *et al.*, FEV1 (% predicted) was significantly better with omalizumab than with a placebo, with a difference of 2.8% of predicted values⁹. Improvement in FEV1 was 190 ml and 96 ml in the omalizumab and placebo groups, respectively. It should be noted that in previous randomized controlled trials, responders and non-responders were discriminated prospectively.

Accepted Article

In the present real-life study, we observed a pre-bronchodilator improvement of 7.7% in responders to omalizumab at 6 months and a decrease of 7.0 % in non-responders. In previous real-life studies, pre-bronchodilator FEV1 improvement ranged from 6.4% to 21% at 4 months^{18-20,25}. Only one study has assessed responders and non-responders to omalizumab separately²⁵. At 4 months, the FEV1 improvement in responder patients was 15.9%, but a greater FEV1 improvement was observed in non-responders²⁵. One possible explanation of this surprising result is that the non-responder group included some moderate responders to omalizumab. In our study, by contrast, we found a clear FEV1 decrease in non-responders.

In the present study, we obtained data about the evolution of pre- and post-bronchodilator FEV1 over a period of 2 years in responders to omalizumab. The FEV1 improvement was found at 6 months and remained stable thereafter. Previous real-life studies found an FEV1 improvement of 9.9% and 22.4% at 2 years, 33.3% at 3 years, 24.5% at 4 years, 34% at 7 years^{20,25-28}. Only one study reported FEV1 at 4 months which appeared to remain stable between 4 months and 4 years²⁰.

We also found an FEF25%-75% improvement at 6 months in responders to omalizumab which was 9.2%, compared to a decrease of 15.5% in non-responders. Like FEV1, this improvement in responders remained stable for 2 years. FEF25%-75% is one of the most popular indices of peripheral airway obstruction²⁹. It has previously been suggested that omalizumab could have an anti-inflammatory effect on small airways³⁰. In one study, assessment by computed tomography revealed that airway-wall thickness reduced significantly 48 weeks of omalizumab treatment (no significant changes were found at 16 weeks). In that study, FEF 25%-75% was not influenced by omalizumab, but only a small sample of patients was evaluated. In another study, omalizumab did not lower the alveolar NO concentration (CalvNO), which could reflect small airway inflammation³¹. However, the

authors concluded that the model they used may not have been sufficiently sensitive to detect small changes in CalvNO.

Over the period of 2 years, we found a decrease in RV and RV/TLC ratio at 6 months but no significant change in TLC. After 6 months, RV worsened a little but RV/TLC remained stable. RV is higher in patients with air trapping, a phenomenon observed in part in peripheral airway alterations^{16,32}. An increase in RV and RV/TLC is a marker of hyperinflation and air trapping, which could be an indication of peripheral airway disease. Interestingly, in our study, we observed significantly greater RV improvement in patients with severe airway obstruction ($FEV1 \leq 50\%$) than in those with less obstruction. These patients may have a lung hyperinflation that could reflect air trapping and small airway obstruction³³. Specific effects of omalizumab on small airways should be assessed in further studies and it would be interesting to perform forced oscillation technique and CT imaging of pulmonary ventilation in a large sample of asthmatic patients treated with omalizumab.

Our study has several limitations. First, in the baseline characteristics, the pre-bronchodilator FEV1 in non-responders was statistically lower than in responders. The proportion of patients with $FEV1 < 50\%$ was also statistically higher. This can at least partly be explained by the “real-life” design of our study and the lack of randomization. It could also reflect a more severe airway obstruction in non-responders. However, in the multivariate logistic regression analysis, pre-bronchodilator FEV1 was not identified as a discriminating marker of omalizumab response. By contrast, Bousquet *et al.* found severe FEV1 as a positive predictor for omalizumab response³⁴. However, this result was never confirmed and, the study was not designed to address this specific issue. Moreover, at baseline, before omalizumab treatment, GERD was statistically higher in non-responders compared with responders. It has been shown that nocturnal GERD is associated to airflow obstruction and could explain the difference observed in terms of FEV1³⁵. It has been suggested that GERD-

related asthma could be a distinct phenotype compared with the allergic phenotype³⁶. Patients with GERD-related asthma may have a lower response to omalizumab but as suggested by our statistical analysis, GERD does not seem to be a marker of omalizumab response. Secondly, although omalizumab prescription is restricted to patients with perennial allergies in Europe, 13.4% and 4.7% of responders and non-responders are not sensitized to allergens. These numbers are close to the number found in a recent study performed in UK³⁷. This reflects the “real-life” design of the studies. Indeed, recent data suggest a potential effect of omalizumab in nonatopic patients³⁸. For this reason, some physicians can have opted for omalizumab to control non-allergic severe asthma patients. Moreover, in our study with a real life design, the use of omalizumab as a compassionate drug in severe asthma patients must be pointed out. The assessment of omalizumab use as a compassionate drug is difficult but could have an impact on the difference between responders and non-responders. Thirdly, we assessed ICS adherence only with a self-report measure. An FEV1 improvement with omalizumab could be associated with patients who did not take their ICS properly. In a study assessing the omalizumab effect in patients with poor adherence to ICS, the mean FEV1 value increased by 6% with omalizumab³⁹. Finally, the optimum number of patients, calculated before the study to find a difference in FEV1 between responders and non-responders, was not reached. Despite this fact, a statistical difference was found in the pre- and post-bronchodilator FEV1 between responders and non-responders.

CONCLUSION

In conclusion, PFT improved in patients with omalizumab. At 6 months, pre- and post-bronchodilator FEV1 was statistically different between omalizumab responders and non-responders with an improvement in responders and a decrease in non-responders. The FEF 25%-75% change was also better in responders than in non-responders. After an increase,

FEV1 and FEF 25%-75% remained stable over a period of 2 years. RV, but not TLC, improved at 6 months and remained stable for 2 years. The mechanism of omalizumab in the improvement of PFT remains to be elucidated. The effect of omalizumab on small airways in severe asthmatic patients should be investigated in further studies.

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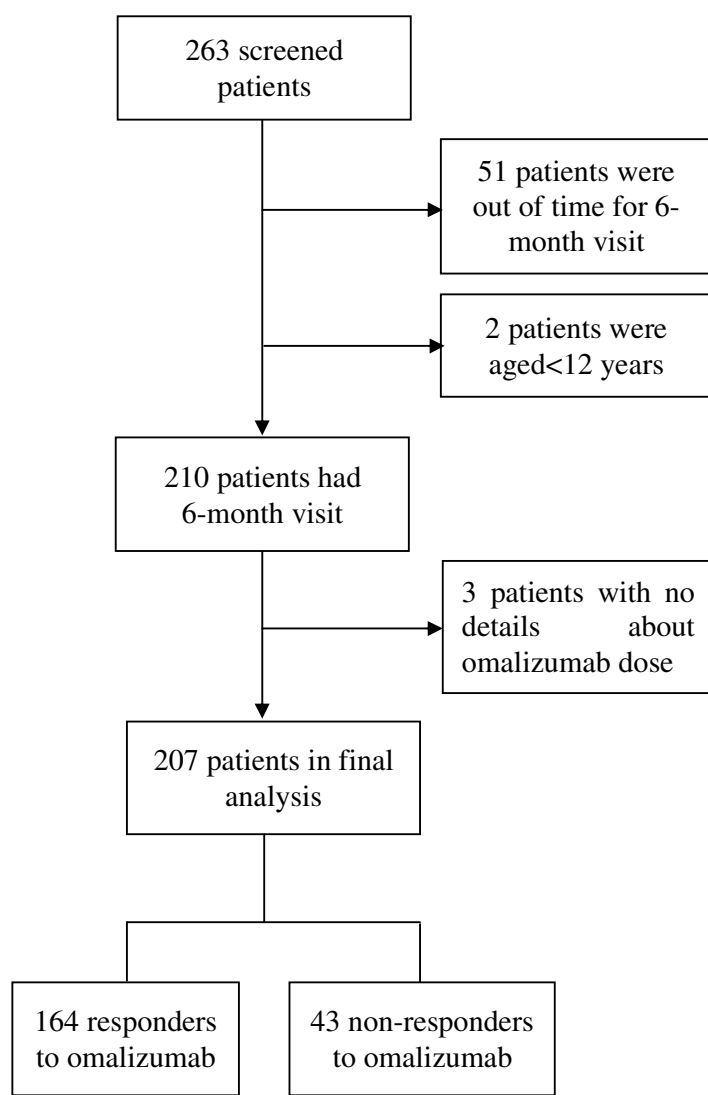


Figure 1: Study flow chart. Number of patients who were screened, enrolled, assigned to omalizumab non responders and responders in final study.

Table 1: Baseline clinical and biological characteristics of the study population.

	Total population n=207	Omalizumab non- responders n=43	Omalizumab responders n=164	p-value
Female (%)	61.8	51.2	64.4	NS
Age (years)	50.0±15.2	51.0 ± 14.1	49.8 ± 15.5	NS
Body mass index (kg/m ²)	26.1±5.3	25.5 ± 5.3	26.3 ± 5.3	NS
Age of asthma onset	23.2±14.2	22.1 ± 16.8	23.6 ± 13.3	NS
Allergen sensitization	89.9	95.3	86.6	NS
Former- or active- smokers	14.4	16.3	11.6	NS
Aero-contaminants exposure (%)	9.2	9.3	9.1	NS
Diurnal symptoms (%)	98.5	100.0	98.2	NS
Nocturnal symptoms (%)	87.6	97.7	85.4	<0.05
Rhinitis (%)	48.3	41.9	50.0	NS
Polyposis (%)	17.4	23.3	15.9	NS
GERD (%)	33.3	51.2	28.7	<0.01
Use of β2-agonists rescue (%)	95.6	100.0	94.5	NS
β2-agonists rescue more than 4 times a week (%)	52.9	62.8	50.3	NS
Patients with one or more exacerbations/year (%)	95.6	95.3	95.7	NS
Patients with two or more exacerbations/year (%)	51.5	51.2	51.6	NS
Rate of exacerbations/year	4.3±2.3	4.9±2.8	4.1±2.1	NS
LABA use (%)	91.3	95.3	90.2	NS
ICS dose (µg/d)	2398 ± 1033	2716 ± 1283	2315 ± 945	<0.05
Oral corticosteroid use (%)	42.5	48.8	40.9	NS
Mean dose/day (mg)	21.2±16.2	26.1±18.2	19.2±14.7	NS
Total IgE (UI/ml)	516.6±865.8	437.8±593.7	536.8±923.3	NS
Omalizumab dose (mg/2 weeks)	372.3 ± 131.6	393.8 ± 147.8	367.7 ± 128.3	NS
Omalizumab dose (mg/4 weeks)	257.7 ± 89.1	241.3 ± 108.3	262.0 ± 84.0	NS

Values are mean ± SD for quantitative data and percentages for qualitative data. LABA=Long Acting Beta2 Agonist, ICS=Inhaled Corticosteroids, IgE=Immunoglobulin E, FEV1=Forced Expiratory Volume in 1 second. Lung function parameters are expressed in liters (% of predicted values).

Table 2: Functional baseline characteristics of omalizumab responders and non-responders at 6 months.

	Omalizumab non-responders n=43	Omalizumab responders n=164	p-value
Pre-bronchodilator FEV1 (L)	1.8 ± 0.8	1.9 ± 0.8	NS
Pre-bronchodilator FEV 1 (% of predicted value)	59.3 ± 20.4	67.4 ± 20.1	<0.05
Post-bronchodilator FEV1 (L)	1.8 ± 0.7	2.0 ± 0.7	NS
Post-bronchodilator FEV1 (% of predicted value)	63.4 ± 19.9	69.7 ± 18.8	NS
Difference between pre- and post-bronchodilator (L)	0.1 ± 0.2	0.2 ± 0.3	NS
Difference between pre- and post-bronchodilator (% of predicted value)	5.6 ± 6.1	6.1 ± 8.5	NS
VC (L)	2.9±0.9	2.7±1.0	NS
VC (% of predicted value)	77.8±17.1	80.2±20.4	NS
FEV1/VC	0.6±0.2	0.7±0.2	<0.05
% patients with FEV1/FVC ratio < 0.7	69.7	54.1	NS
FEF25%-75% (L/sec)	1.4 ± 0.9	1.5 ± 1.1	NS
% patients with FEV1<50% predicted value	39.5	19.5	<0.01
FEF25%-75% (% of predicted value)	38.9 ± 24.7	44.4 ± 29.4	NS
TLC (L)	5.4 ± 1.2	5.4 ± 1.4	NS
TLC (% of predicted value)	101.6 ± 15.8	99.4 ± 18.4	NS
RV (L)	2.5 ± 0.9	2.6 ± 1.0	NS
RV (% of predicted value)	139.3 ± 50.0	138.3 ± 46.4	NS
RV/TLC	1.4 ±0.4	1.4 ±0.3	NS

Values are mean ± SD for quantitative data and percentages for qualitative data. FEV1=Forced Expiratory Volume in 1 second, VC=Vital Capacity, FVC=Forced Vital Capacity, FEF=Forced expiratory flow 25% to 75%, TLC=Total Lung Capacity, RV=Residual volume.

Table 3: Changes in lung function parameters at 6 months in omalizumab responders and non-responders.

	Omalizumab non-responders n=43	Omalizumab responders n=164	p-value
Pre-bronchodilator FEV1 (L)	-0.1 ± 0.4	0.2 ± 0.4	<0.01
Pre-bronchodilator FEV 1 (% of predicted value)	-3.9 ± 13.3	5.7 ± 13.7	<0.001
Post-bronchodilator FEV1 (L)	-0.1 ± 0.4	0.1 ± 0.3	<0.01
Post-bronchodilator FEV1(% of predicted value)	-5.2 ± 15.0	5.1 ± 12.5	<0.01
Difference between pre- and post-bronchodilator (L)	-0.0 ± 0.3	-0.0 ± 0.3	NS
Difference between <i>pre-</i> and post-bronchodilator (% of predicted value)	-0.8 ± 9.6	-1.4 ± 6.9	NS
VC (L)	0.0 ± 0.4	0.1 ± 0.6	NS
VC (% of predicted value)	-1.0 ± 13.2	4.6 ± 16.7	NS
FEV1/FVC	0.0 ± 0.1	0.0 ± 0.2	NS
FEF (L/sec)	-0.2 ± 0.6	0.2 ± 0.7	<0.01
FEF (% of predicted value)	-5.3 ± 14.7	4.1 ± 17.8	<0.01
TLC (L)	-0.3 ± 0.8	0.0 ± 0.7	NS
TLC (% of predicted value)	-7.1 ± 16.2	-0.9 ± 16.8	NS
RV (L)	-0.2 ± 1.0	-0.2 ± 0.7	NS
RV (% of predicted value)	-9.4 ± 56.8	-12.2 ± 39.7	NS

Values are mean ± SD differences between baseline and 6 months. FEV1=Forced Expiratory Volume in 1 second, VC=Vital Capacity, FVC=Forced Vital Capacity, FEF=Forced Expiratory Flow 25% to 75%, TLC=Total Lung Capacity, RV=Residual Volume.

Table 4: Lung function parameters at baseline, 6, 12 and 24 months in omalizumab responder patients.

	Baseline	6 months	12 months	24 months	p-value
Pre-bronchodilator FEV1 (L) (n=147)	1.9 ± 0.7	2.1 ± 0.8	2.0 ± 0.8	2.0 ± 0.8	<0.0001
Pre-bronchodilator FEV1 (% of predicted value) (n=147)	67.7 ± 19.5	73.0 ± 20.3	71.8 ± 21.4	72.3 ± 21.3	<0.0001
Post-bronchodilator FEV1 (L) (n=64)	2.0 ± 0.7	2.1 ± 0.7	2.0 ± 0.6	2.0 ± 0.7	<0.01
Post-bronchodilator FEV1(% of predicted value) (n=57)	69.8 ± 18.1	74.9 ± 19.0	72.4 ± 18.7	75.3 ± 20.7	<0.001
<i>Difference between pre- and post-bronchodilator (L) (n=63)</i>	0.2 ± 0.3	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	NS
<i>Difference between pre- and post-bronchodilator (% of predicted value) (n=57)</i>	6.5 ± 8.4	4.9 ± 5.1	6.0 ± 6.5	5.1 ± 5.2	NS
% of patients with FEV1<50% (n=147)	15.7%	15.0%	17.0%	13.6%	NS
VC (L) (n=87)	2.8 ± 0.9	2.9 ± 0.9	2.8 ± 0.9	2.8 ± 1.0	NS
VC (% of predicted value) (n=87)	80.8 ± 21.2	85.6 ± 20.6	82.6 ± 20.4	83.9 ± 21.1	<0.05
FEV1/FVC (L) (n=87)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	NS
% of patients with FEV1/FVC ratio < 0.7 (n=87)	55.2%	54.0%	54.0%	44.8%	<0.05
FEF (L/sec) (n=136)	1.5 ± 1.0	1.7 ± 1.2	1.7 ± 1.2	1.7 ± 1.2	<0.01
FEF (% of predicted value) (n=136)	44.5 ± 29.4	48.5 ± 29.8	48.1 ± 30.5	48.2 ± 31.1	<0.05
TLC (L) (n=85)	5.4 ± 1.4	5.3 ± 1.4	5.3 ± 1.5	5.4 ± 1.4	NS
TLC (% of predicted value) (n=85)	101.0 ± 18.0	98.9 ± 17.8	99.0 ± 18.6	102.1 ± 16.8	NS
RV (L) (n=88)	2.6 ± 0.9	2.4 ± 0.9	2.5 ± 1.1	2.6 ± 0.9	<0.05

RV (% of predicted value) (n=88)	141.4 ± 44.1	126.9 ± 38.5	133.8 ± 46.2	138.3 ± 36.2	<0.05
RV/TLC (n=85)	1.4 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	<0.01

Values are mean ± SD for quantitative data and percentages for qualitative data. FEV1=Forced Expiratory Volume in 1 second, VC=Vital Capacity, FVC=Forced Vital Capacity, FEF=Forced Expiratory Flow 25% to 75%, TLC=Total Lung Capacity, RV=Residual Volume.