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Severe non-atopic asthma: omalizumab can reduce severe asthma exacerbations

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ABSTRACT

Introduction: Humanized monoclonal anti-IgE antibody (omalizumab) has demonstrated efficacy in severe atopic asthma. However, few studies have assessed its efficacy in non-atopic and even less in T2-low severe asthma. The objective was to determinate the omalizumab response according to atopic status.

Methods: This retrospective, real-world study was performed in the Chest Diseases Department of Strasbourg University Hospital from January 1, 2006, to June 30, 2017. The response to omalizumab was assessed in 139 patients 4, 6, and 12 months after treatment and compared to data collected prior to omalizumab initiation.

Results: Forty-four patients (31.7%) had severe non-atopic asthma and 95 (68.3%) had a severe atopic asthma. In the non-atopic group, omalizumab significantly reduced the severe exacerbation rate by 44% (95% CI 18–64%, $p < 0.05$), 43% (CI 95% 20–60%, $p < 0.05$), and 54% (CI 95% 36–67%, $p < 0.05$), at 4, 6 and 12 months, respectively. A trend toward improvement in FEV1, asthma control and oral corticosteroid use was also observed. These results were not significantly different from those obtained in atopic asthmatics except a more effective oral corticosteroid sparing in atopic group ($p < 0.05$). Similar reduction of severe exacerbation rates were observed in T2-low asthma subgroup (non-atopic, non-eosinophilic).

Conclusion: Omalizumab was effective in severe asthma, regardless of atopic status.

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Severe asthma; atopy; T2 inflammation; eosinophil; omalizumab

Introduction

Between 3 and 10% of asthmatics have severe asthma (1). Omalizumab is a humanized monoclonal anti-IgE antibody, that decreases the levels of circulating IgE by binding to the constant region of the IgE molecule, preventing the IgE interaction with the IgE receptor on inflammatory cells and leading to downregulation of FcεRI expression (2). Omalizumab is recommended for patients who have a positive skin prick test (SPT) or serum IgE to a perennial aeroallergen, with reduced lung function (forced expiratory in 1 s [FEV1] < 80% of predicted value) that is not adequately controlled despite high-dose inhaled corticosteroids and long-acting β₂-agonists according to Global Initiative for Asthma (GINA) step 4 or 5 (3). Anti-IgE treatment has demonstrated efficacy in reducing the asthma exacerbation rate, decreasing systemic corticosteroid use, and improving asthma control and quality of life in atopic severe asthma (3–7). The

treatment also has an acceptable safety and good adherence profile (8,9).

Omalizumab was the first biological drug available for the treatment of severe asthma. However, the prevalence of non-atopic severe asthma in adults was estimated to be 50% in the European Network For Understanding Mechanisms Of Severe Asthma (ENFUSOMA) study and 17–34% in the Severe Asthma Research Programme (SARP) study (10,11). Some studies have demonstrated similarities in the immunopathology of atopic asthma and non-atopic asthma. The number of FcεRI+ cells (mast cells and macrophages), type 2 (T2) cytokines (interleukins [IL]-4, IL-5, and IL-13), and IgE levels in the bronchial mucosa are increased in asthmatic patients regardless of their atopic status (12–14). Aeroallergens as well as viral antigens and staphylococcal enterotoxins, can induce maturation and migration of Th2 cells, local production of IL-4 and IL-13, and B-cell

switching to produce IgE antibodies (14,15). Non-atopic and atopic asthma are associated with IgE production in the bronchial mucosa (14). Thus, omalizumab therapy can be effective in severe non-atopic asthma.

Recently, novel therapies targeting IL-5 and IL-4/IL-13 have emerged for the treatment of severe eosinophilic asthma. Among patients with T2 endotypes, approximately 50% of severe asthma cases have an overlapping syndrome (*i.e.* patients with atopic status and eosinophil count $\geq 300/\text{mm}^3$) (16), and physicians have a choice between anti-IL-5, anti-IL-4/IL-13 or anti-IgE. We explored the response to omalizumab regardless of the pretreatment blood eosinophil count. However, few therapeutic methods can be used for T2-low asthma (17), so we considered effect of anti-IgE treatment for these patients.

The aim of the present study was to compare the effectiveness of omalizumab in a non-selected population of severe non-atopic asthmatics and severe atopic asthmatics.

Materials and methods

Study design and patients

This single-center, retrospective, real-life study was conducted in the Chest Diseases Department of Strasbourg University Hospital from January 1, 2006, to June 30, 2017.

Inclusion criteria were any uncontrolled severe asthma according to the 2018 GINA guidelines despite daily high-dose inhaled corticosteroid treatment (1000 µg beclomethasone dipropionate or equivalent per day) plus a LABA with or without maintenance oral corticosteroid, treated with omalizumab. All patients followed in the department 12 months prior omalizumab treatment, with a clinical evaluation at 4 (T4), 6 (T6), and 12 months (T12) of omalizumab treatment were included. All omalizumab injections were performed in our department. Patients with incomplete medical data or patients who refused collection of their medical data were excluded.

The baseline data included age, sex, body mass index (BMI), smoking history (smoker/ex-smoker > 10 pack-years), characteristics of the asthma (asthma control according to GINA 2018, number of severe exacerbations as defined by the ERS/ATS statement (18), 12-month period prior to omalizumab, FEV1, presence of nasal polyposis), total serum IgE, blood eosinophil count, and allergic status documented by SPT for common aeroallergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Aspergillus*

fumigatus, *Alternaria alternata*, cat and dog dander, cockroaches, pollens (birch, ash, plane and grass). Non-atopic asthma was defined by a negative SPT. T2-low asthmatics were defined as having no positive skin tests to aeroallergens and eosinophil count $\leq 300/\text{mm}^3$. Medications were also recorded (use of oral glucocorticosteroids). The dose (in milligrams) and dosing frequency (every 2 or 4 weeks) of omalizumab were based on total serum IgE levels (kU/L) and body weight (in kilograms) as recommended by Novartis.

This study was approved by the Institutional Board of Strasbourg University Hospital (CE-2021-75).

Outcome measures

The response to omalizumab treatment was assessed at T4, T6, and T12 and compared to data collected at baseline, before omalizumab initiation. The comparison was based on four criteria: reduction in the rate of severe asthma exacerbation, decreased oral glucocorticoid use, improved asthma control, and improvement in FEV1. FEV1 was determined only at 6 and 12 months, whereas changes in oral glucocorticoid use were based on the percentage of patients using them at the various time points. The annual severe asthma exacerbation rate was determined, by changes to the number of exacerbations over a 12-month period. Severe asthma exacerbation was defined as a deterioration of asthma leading to treatment with oral corticosteroids or 50% increase in the usual dose ≥ 3 days, or hospitalization or emergency department visit leading to treatment with systemic oral corticosteroids (19). Improved asthma control was based GINA 2018. Patients were classified into two groups: well controlled asthma and not controlled (including partly controlled and uncontrolled asthma). The causes for discontinuing treatment were also evaluated.

Statistical analysis

The categorical variables were described by the frequencies and proportions (n, %) of their modalities. Quantitative variables were described by mean [SD] if the distribution was Gaussian, median and interquartile range [IQR] otherwise. The normality of the distribution of quantitative variables was checked graphically.

Continuous judgment criteria were modeled using linear regression models for quantitative variables, such as FEV1, or Poisson regression models for counts, such as the number of exacerbations, with an offset over the collection period when the periods

differed. A random effect was placed on the intercept to account for repeated data from the same subject. A group/treatment interaction factor was formulated to estimate a difference in treatment effect depending on the group. The results are presented as regression coefficients or odds ratios (ORs) and their 95% confidence intervals (CIs).

The significance was set at 5%.

Results

Patients

From January 1, 2006, to June 30, 2017, 181 patients were treated with omalizumab for severe asthma; 139 of them were included in the study. Forty-two patients

were excluded due to incomplete medical data or because they were not followed by our team (Figure 1).

At T4 and T6, 96% ($n=133$) and 83% ($n=116$) patients, respectively, were still treated with omalizumab, compared to 64% ($n=89$) at T12. At baseline, the patient characteristics were similar between those who continued omalizumab more than 12 months and those who stopped it before 12 months. Lack of improvement was the most common cause for discontinuation of omalizumab (26%, $n=36/139$). Only 12 patients discontinued omalizumab due to adverse effects, the most frequent of which were headaches. Less than one-fourth of patients with atopic asthma stopped omalizumab due to lack of efficacy 23.1%, ($n=22/95$) compared to 31.8% ($n=14/44$) of patients with non-atopic asthma ($p=0.3$).

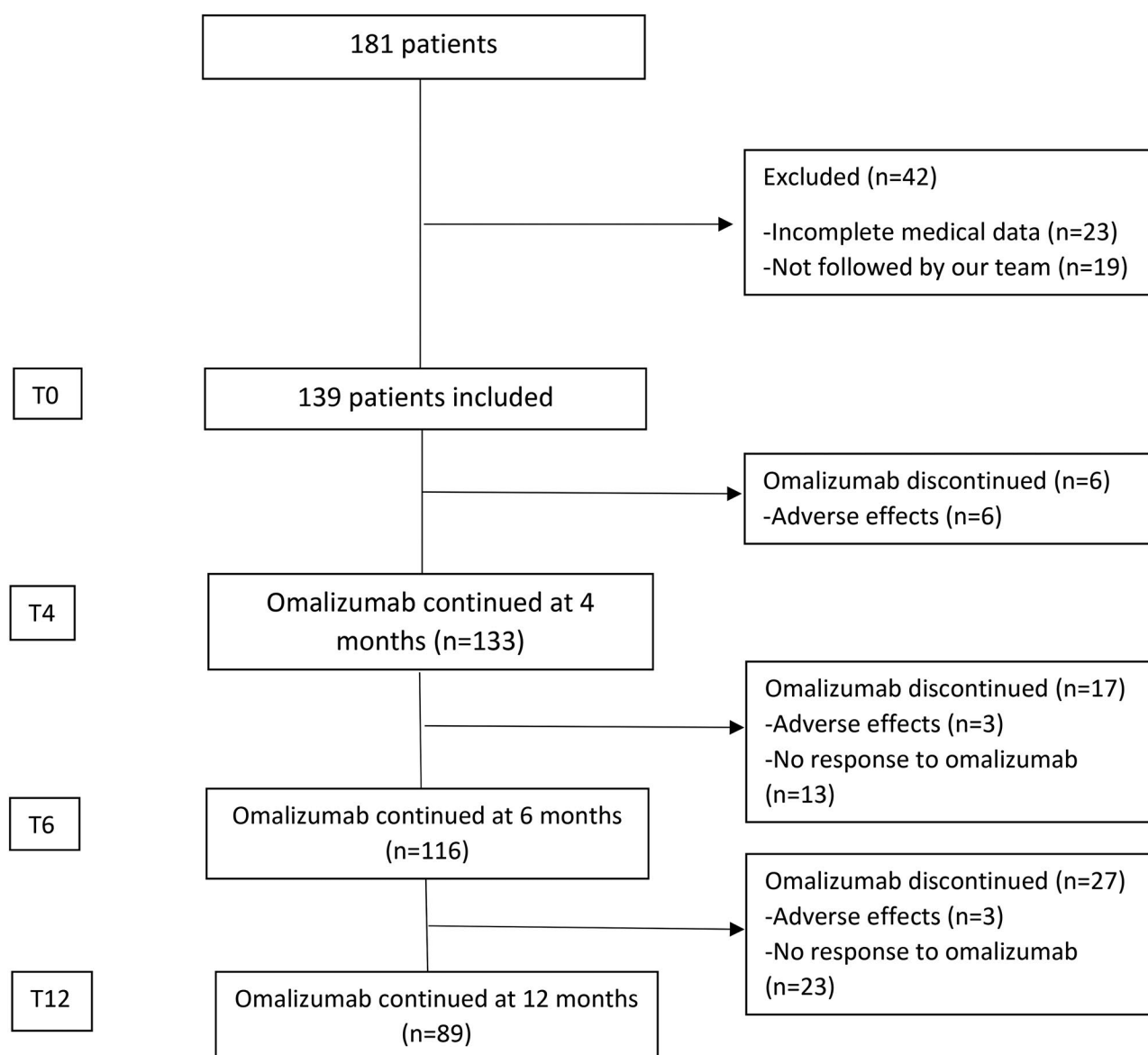


Figure 1. Study flowchart.

Of the 139 patients, 31.7% ($n=44$) had severe non-atopic asthma and 68.3% ($n=95$) had severe atopic asthma (31.6% of atopic patients had > 4 positive SPTs and 67.4% were sensitized to *Dermatophagoides pteronyssinus* and/or *farinae*).

All patients had uncontrolled asthma, with a mean $\pm$ SD rate of severe exacerbations in the prior year of 3.48 ± 2.95 . Continuous oral corticosteroids were used in 34.5% of patients and the mean $\pm$ SD FEV1 was $68.5 \pm 21.4\%$ of the predicted value.

The baseline characteristics of the atopic and non-atopic patients are compared in Table 1. Characteristics were similar in both groups, except total serum IgE levels and the omalizumab dose were significantly higher in the atopic group, and nasal polyps and treatment with maintenance oral corticosteroids were more frequent in the non-atopic group ($p < 0.05$).

In the atopic group, 39.8% of patients had a blood eosinophil count $\geq 300/\text{mm}^3$. Blood eosinophil data were not available for seven patients. At T0, total IgE levels were higher in the high eosinophil group (median [IQR] 720 [268.5–1434] kU/L *versus* 176 [87–458] kU/L; $p < 0.05$), except this data, all other characteristics were similar.

Severe exacerbations

Omalizumab significantly reduced the severe exacerbation rate by 47% (95% CI 33–58%, $p < 0.05$), 48% (95% CI 36–58%, $p < 0.05$) and 55% (95% CI 45–63%, $p < 0.05$) at T4, T6 and T12, respectively compared to the 12-month pretreatment period. The mean $\pm$ SD

annual exacerbation rate was 3.48 ± 2.95 before treatment *versus* 1.83 ± 2.78 at T4; 1.83 ± 2.58 at T6; and 1.63 ± 1.89 at T12. The reduction was not significantly different between atopic and non-atopic group ($p = 0.72$, $p = 0.51$, and 0.52 , at T4, T6, and T12, respectively). (Figure 2). The annual rate of exacerbations on average was the same in both groups; after 12 months of treatment, the mean reduction in the exacerbation rate was 55% in the atopic group and 54% in the non-atopic group.

In the atopic group, the exacerbation rate was significantly reduced in patients with an eosinophil count $\geq 300/\text{mm}^3$, ($p < 0.05$) and in patients with an eosinophil count $< 300/\text{mm}^3$, ($p < 0.05$), without a significant difference between them during the 12 months of treatment ($p = 0.3$ at T4, $p = 0.6$ at T6 and $p = 0.8$ at T12). Reduction in the asthma exacerbation rate according to the blood eosinophil count in patients with severe atopic asthma is shown in Table 2.

Oral corticosteroid use

At T0, 34.5% ($n = 48/139$) of patients were treated with oral corticosteroids (mean $\pm$ SD daily dose 20.4 ± 13.3 mg/day), compared to 25.6% at T4 ($p < 0.05$), 21.6% at T6 ($p < 0.05$), and 19.1% at T12 ($p < 0.05$). The proportion of patients under glucocorticosteroid treatment decreased in atopic patients (28.4% at T0 *versus* 17.8% at T4, $p < 0.05$; 11.7% at T6, $p < 0.05$ and 11.5% at T12, $p = 0.07$), but also in non-atopic patients (47.7% at T0 *versus* 41.9% at T4, ($p = 0.37$); 41% at T6, ($p = 0.22$) and 35.7% at T12, ($p < 0.05$)). However, more patients were treated with glucocorticosteroids

Table 1. Patients characteristics.

	Non-atopic $n=44$	Atopic $n=95$	P-value
Age at omalizumab initiation (years)	53.9 ± 14.4	51.4 ± 14.8	0.34
Sex,			
Female	28 (63.6)	49 (51.2)	
Male	16 (36.4)	46 (48.4)	0.2
BMI (kg/m^2)	25 [21.8–31]	25 [22–31]	0.8
Smoker or ex-smoker (≥ 10 pack-years)	17 (38.6)	33 (34.7)	0.79
Nasal polyps	18 (40.9)	17 (17.9)	< 0.05
GINA			
Step 4	8 (18.2)	18 (18)	
Step 5	36 (81.8)	77 (81.1)	0.99
Blood eosinophils (cells/mm^3)	230 [160–510]	250 [158.3–475]	0.77
Total serum IgE (kU/L)	66.5 [25.3–202.3]	320 [113.3–762.8]	< 0.05
Exacerbations in prior 12 months	3.5 ± 2.88	3.47 ± 3	0.96
Asthma control	0 (0)	0 (0)	
Oral corticosteroid	21 (47.7)	27 (28.4)	< 0.05
Dose (prednisone equivalent mg/day)	20 [10–20]	20 [10–25]	0.24
Dose of ICS (BDP equivalent $\mu\text{g}/\text{day}$)	2 000 [1 000–2 125]	2000 [1 000–3 500]	0.13
FEV1 (mL)	$1\,958 \pm 833$	$2\,013 \pm 842$	0.72
FEV1 (% of predicted value)	72 ± 23.4	66.9 ± 20.4	0.2
FEV1/FVC	0.67 ± 0.11	0.69 ± 0.13	0.3
Dose of omalizumab (mg/month)	150 [150–300]	600 [300–825]	< 0.05

Data are presented as mean $\pm$ standard deviation, n (%), or median [interquartile range].

BMI = body mass index; ICS = inhaled corticosteroid; BDP = beclomethasone dipropionate;

FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

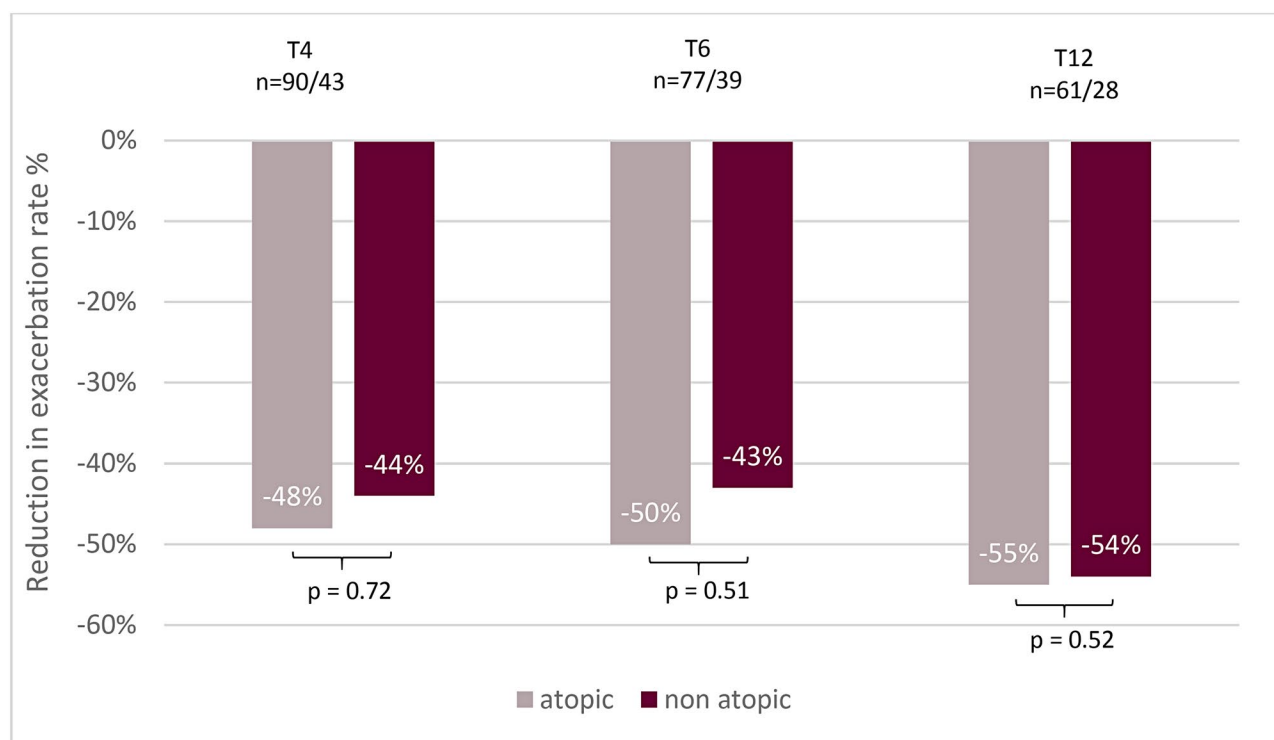


Figure 2. Reduction in asthma exacerbation rate according to atopic status compared to the year to prior omalizumab introduction.

Table 2. Asthma exacerbation rate according to blood eosinophil count in patients with severe atopic asthma compared to the year prior to omalizumab introduction.

	Eosinophils $\geq 300/\text{mm}^3$	Eosinophils $< 300/\text{mm}^3$	Difference between two groups
T0 (n = 35/53)	3.7 $\pm$ 3.5	3.3 $\pm$ 2.7	p = 0.3
T4 (n = 33/50)			p = 0.6
Annual exacerbation rate	2.7 $\pm$ 4.1	2.2 $\pm$ 3.3	
Annual rate change	-46 [-67; -16]**	-47 [-65; -22]**	
T6 (n = 31/39)			p = 0.54
Annual exacerbation rate	1.9 $\pm$ 3.4	1.5 $\pm$ 1.9	
Annual rate change	-48 [-67; -24]**	-52 [-68; -30]**	
T12 (n = 21/33)			p = 0.8
Annual exacerbation rate	1.4 $\pm$ 1.8	1.5 $\pm$ 2	
Annual rate change	-62 [-76; -42]**	-54 [-67; -37]**	

Data are presented as mean $\pm$ standard deviation with the reduction in annual rate change % [95% confidence interval].

**Significant difference compared to baseline data.

at T0 in the non-atopic group, but also at T4, T6, and T12 ($p < 0.05$). (Figure 3).

At baseline, the proportion of patients treated with glucocorticosteroids were 40% in atopic and high eosinophil group *versus* 24.5% in atopic and low

eosinophil group ($p = 0.19$). A significant decrease in oral corticosteroid use occurred only at T4 (21.2%, $p < 0.05$ compared to baseline) and T6 (12.9%, $p < 0.05$ compared to baseline) in atopic patients with blood eosinophil count $\geq 300/\text{mm}^3$.

Asthma control

Asthma control was achieved in 28.6%, 48.3%, and 58.4% of patients at T4, T6 and T12, respectively. At T12, the percentage of atopic patients with well-controlled asthma was 59% compared to 57.1% in the non-atopic group ($p = 0.99$). In the atopic group, asthma control was improved regardless of blood eosinophil count (OR 1.11 95% CI 0.74–1.66, $p = 0.6$ at T4; OR 1.22 95% CI 0.65–2.3, $p = 0.54$ at T6 and OR 0.87 95% CI 0.31–2.47, $p = 0.8$ at T12).

Respiratory function

The mean FEV1 significantly improved after 6 and 12 months of treatment compared to baseline only in atopic patients (+171 ml at T6 and +223 ml at T12, $p < 0.05$), but no significant difference was observed between the two groups at T6 ($p = 0.46$) and T12 ($p = 0.34$). (Figure 4). A trend toward improvement in FEV1 was also observed in atopic group with high and low eosinophils subgroups.

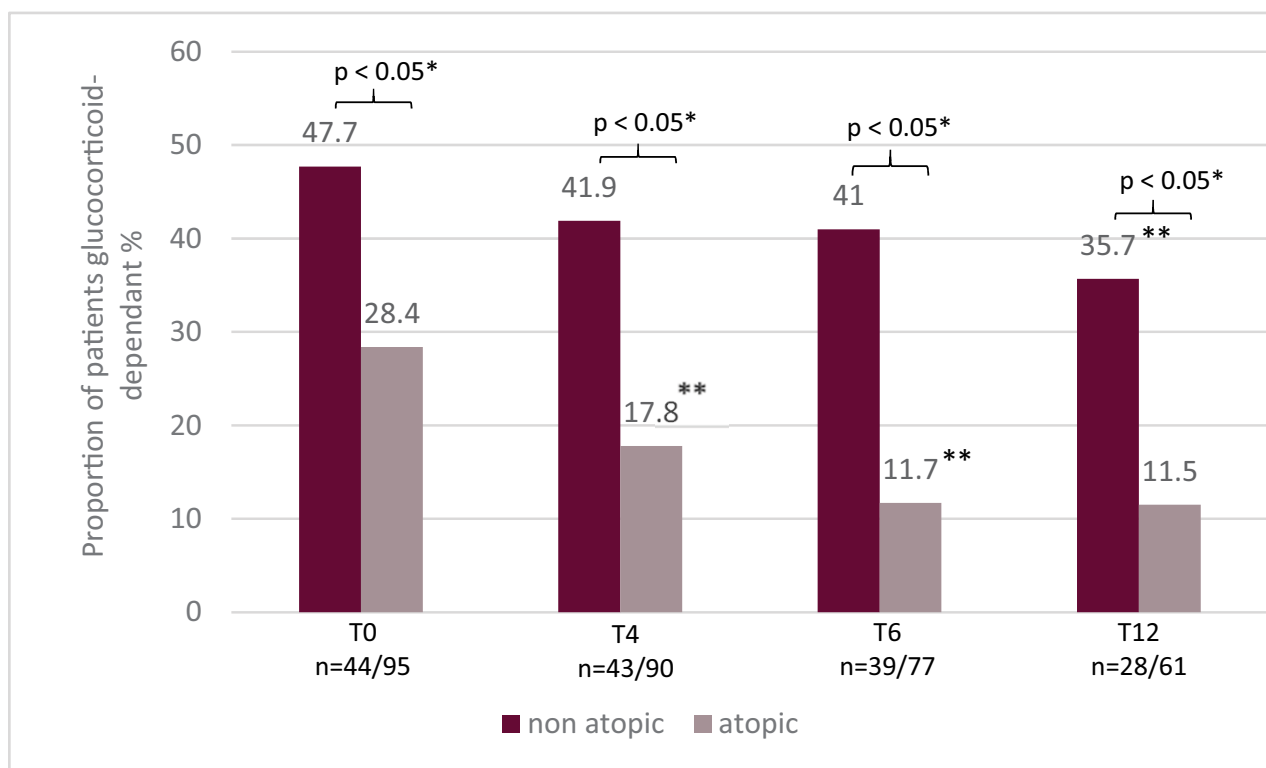


Figure 3. Proportion of glucocorticoid-dependent patients.* Significant difference between atopic and non-atopic patients** Significant difference compared to baseline data.

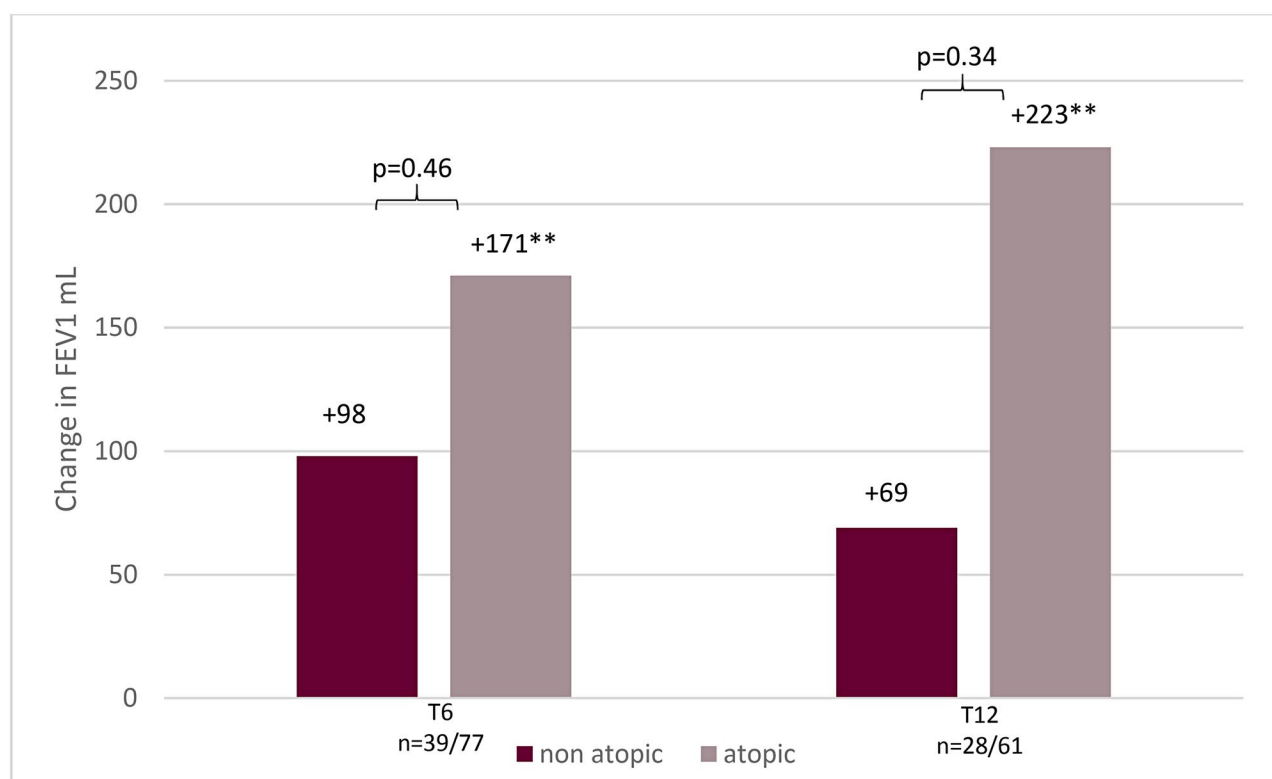


Figure 4. Change in FEV1 compared to baseline data according to atopic status.** Significant difference compared to baseline data.

T2 low-asthma

Among the 44 non-atopic patients, 57% ($n=25/44$) had a blood eosinophil count $< 300/\text{mm}^3$. Omalizumab reduced the severe exacerbation rate by 38% (95% CI -2 – 64% , $p=0.07$), 38% (95% CI 3 – 62% , $p<0.05$) at T6 and 47% (95% CI 19 – 66% , $p<0.05$) at T12 in the T2-low group (*i.e.* non-atopic and non-eosinophilic asthma). Compared to atopic patients, T2-low asthmatic patients were older (mean $\pm$ SD 58.7 ± 10.22 versus 51.5 ± 15.2 years, $p<0.05$), were more often treated with glucocorticosteroids (56% versus 30.7%, $p=0.037$), and had lower IgE levels (median [IQR] 37 [21–119] kU/L versus 300 [111.5–736.5] kU/L, $p<0.05$). We observed a trend of no difference in severe asthma exacerbations between atopic and T2-low asthma during the treatment period (OR 1.16, 95% CI 0.62–2.08, $p=0.64$ at T4; OR 1.24, 95% CI 0.71–2.11, $p=0.43$ at T6; and OR 1.21, 95% CI 0.73–1.99, $p=0.45$ at T12).

Discussion

This study suggests that omalizumab treatment has efficacy in severe asthma regardless of atopic status.

Omalizumab is indicated for severe atopic asthma and its efficacy demonstrated, largely in the reduction of severe asthma exacerbations and improved asthma control (3–5). Our results were similar to those obtained in atopic patients, but our cohort included 44 non-atopic asthmatics among 139 patients. Furthermore, a significant reduction in severe asthma exacerbation, an improvement in asthma control, a trend of increased in pulmonary function, and reduction in patients treated with oral corticosteroids were observed in non-atopic patients. These results were not significantly different from those observed in atopic asthma.

Some case reports and a few studies have assessed omalizumab treatment in non-atopic asthma (15,20–22). De Llano et al. compared omalizumab in a population of 29 severe non-atopic asthmatics versus 266 atopic asthmatics: the Global Evaluation of Treatment Effectiveness (GETE) scale, Asthma Control Test (ACT) score, FEV1, and asthma exacerbations were not significantly different between the two groups. All outcomes were significant in the atopic group, whereas only clinical scale (ACT and GETE) were significant in the non-atopic group (20). In a recent *post-hoc* analysis of the real-life FENOMA study, similar results to ours were observed in 80 patients with non-atopic asthma treated with omalizumab (22). Two

randomized controlled clinical trials have explored omalizumab in small cohorts of non-atopic asthmatics. In 2013, Garcia et al. (21) demonstrated an increase statistically in FEV1 and a trend of reduced in asthma exacerbations in patients treated with omalizumab compared to placebo. Later, Pillai et al. proved that omalizumab improves pulmonary function (15).

Previous work (12,13,23) suggests that atopic and non-atopic severe asthma have similar immunopathology profiles and, therefore, omalizumab acts similarly in these two types of asthma. Chanez et al. (24) demonstrated that omalizumab leads to down-regulation of FcεRI expression on basophils and plasmacytoid dendritic cells in atopic asthmatics. Garcia et al. confirmed these results in a population of non-atopic severe asthmatics (21,24). Similarly, omalizumab reduced the number of bronchial mucosal IgE+ cells in both atopic and non-atopic asthmatics (15,25).

In our study, 40% (35 out of 88) of atopic patients had a blood eosinophil count $\geq 300/\text{mm}^3$ as found previously in larger studies (26,27). Outcomes were not significantly different between atopic patients with eosinophils $\geq 300/\text{mm}^3$ and $< 300/\text{mm}^3$. These results confirmed those published in the retrospective Stellair study (26).

The definition of T2-low asthma is still discussed since there is no universally agreed thresholds (17). In our study, 18% ($n=25/139$) of patients had T2-low asthma. We observed that omalizumab reduced the exacerbation rate in this group, without significant difference from atopic patients. These results should be interpreted with care because of the wide confidence interval. For more than 20 years, randomized controlled and real-life trials have demonstrated therapeutic benefits and safety profile of omalizumab. Because few therapeutics are available for T2-low asthma, it would be interesting to perform larger studies to confirm our data.

This study has several limitations. First, it was a single-center retrospective design with a limited number of patients. However, patient characteristics and omalizumab effectiveness were consistent with previous studies (3,5–7). Asthma control was assessed using GINA 2018 guidelines, ACT score would have helped to confirm the asthma control (28).

Only 64% ($n=89/139$) of patients were still being treated at T12, compared to 81% in the Stellair study and 78% in the Experience registry (5,26). The lack of data on patients who stopped treatment because of omalizumab ineffectiveness could be a bias. Excluding the 25.9% ($n=36/139$) of patients who stopped omalizumab due to lack of improvement led

to an over-estimation of the treatment efficacy, and it was more pronounced at T12 because most patients stopped omalizumab after the 6 months. However, no significant differences were found in terms of discontinuation of treatment due to lack of efficacy between the two groups (31.8%, $n = 14/44$ non-atopic patients *versus* 23.1%, $n = 22/95$ atopic patients, $p = 0.3$).

Conclusion

We demonstrated that omalizumab is effective in non-atopic severe asthma in regards to reducing severe asthma exacerbations and achieving asthma control compared to atopic asthma, but also sparing oral corticosteroids after 1 year of treatment. Moreover, in T2 low-asthma (non-atopic with < 300 blood eosinophils/ mm^3), omalizumab significantly reduced severe asthma exacerbation. This could be an interesting development for this medication, as few therapeutic options are currently available for these patients.

Declaration of interest

Conflicts of interest: F. de Blay received financial support from clinical grants from Aimmune, Stallergènes-Greer, ALK, Novartis, AstraZeneca, DBV, Sanofi, and GlaxoSmithKline and has board membership with Aimmune, Stallergènes-Greer, ALK, Novartis, AstraZeneca, DBV, and Sanofi. The rest of the authors declare that they have no relevant conflicts of interest.

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