Real-life study in non-atopic severe asthma patients achieving disease control by omalizumab treatment

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To the Editor,

Severe asthma is defined as asthma requiring treatment with guidelines-suggested medications for Global Initiative for Asthma (GINA) steps 4 or 5 or systemic corticosteroids for [?]50% of the previous year to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy.[1] Up to 34%–50% of severe asthmatic patients have non-atopic (also called non-allergic) asthma. [2] A significant proportion of these patients have severe uncontrolled asthma, which requires high doses of inhaled corticosteroids (ICS) or even oral corticosteroids (OCS).[2] Until the advent of biologics, treatment options in these patients have been very limited. For many years, both the pathogenesis knowledge and the results of clinical trials supported the view that anti-IgE treatment is specifically effective in allergic asthma. Interestingly, recent molecular and clinical evidence suggests that anti-IgE treatment might also be effective in patients with non-allergic asthma.[2] Omalizumab (Xolair®) is an anti-IgE monoclonal antibody that selectively binds to human IgE and prevents the binding of IgE to its receptors. Although omalizumab is indicated in Europe in patients with severe persistent allergic asthma, several case reports and short series have provided data on the value of omalizumab in patients with non-atopic asthma.[3,4]

The observational, multicenter, retrospective, real-life FENOMA study specifically evaluated patients who achieved full asthma control after one year of treatment with omalizumab.[5] The study included 345 patients, 80 (23.2%) of whom had non-atopic asthma. The present *post-hoc* sub-analysis aims to describe the clinical improvement of patients with non-atopic asthma. Socio-demographic and asthma-related characteristics were collected at baseline. Outcomes analyzed at baseline and after one year of treatment were those included in the definition of asthma control by GEMA guidelines.[5] Medical records were reviewed between February 2015 and June 2016. For statistical comparisons, the 2-sided Wilcoxon signed-rank test was used. A P-value of <0.05 was considered to be statistically significant. All analyses were performed with the SAS statistical package (version 9.4; SAS Institute, Cary, NC).

The primary outcome of this *post-hoc* sub-analysis was to describe the baseline characteristics and clinical improvement of non-atopic asthma patients who achieved full disease control after one-year of treatment with omalizumab through i) frequency of daytime symptoms, ii) changes in use of ICS or OCS iii) need for rescue therapy, iv) pulmonary function (forced expiratory volume in 1 second [FEV_1]), v) number of non-severe exacerbations and vi) use of healthcare resources, i.e. unplanned visits to primary care or specialists and the number of days of school or workplace absenteeism due to asthma worsening. Non-severe asthma exacerbations were defined as those that did not require OCS, emergency assistance or hospitalization. Secondary outcomes include an assessment of the percentage of eosinophil blood count and exhaled nitric oxide fraction (FeNO) before and after treatment.

Demographic, clinical characteristics and asthma history (before starting treatment with omalizumab) are shown in **Table 1** . Mean (SD) age of patients was 58.7 (12.2) years and 65% were female. Almost all patients had daytime symptoms, 92% of patients needed rescue medication, and the mean (SD) initial dose of omalizumab was 338.7 (153.1) mg.

After one year of treatment with omalizumab 50.0% (n=40) of patients had no daytime symptoms, while 37.5% (n=30) and 12.5% (n=10) had symptoms 1 and 2 days per week, respectively. Forty-one (51.2%) of the 54 patients who were receiving OCS at entry, stopped treatment (P<0.0001). Of those continuing on OCS, the average reduction of the daily dose was not statistically significant (P=0.2132). More than half of patients (53.7%, n=43) needed no rescue medication. Median FEV_1 increase was 15% and there was a reduction in the number of non-severe asthma exacerbations. After one year of treatment with omalizumab, a great reduction in unplanned visits and absenteeism from school or workplace (P<0.0001; **Table 2**) was observed.

Of note, the effectiveness of omalizumab was previously assessed in a Spanish multicenter registry, which evaluated 29 non-atopic severe asthma patients over 2 years.[6] However, our series is the most extensive study in patients with non-atopic asthma published to date in Spain, and provides data on full disease control. There have been several potential suggestions to explain the effectiveness of omalizumab in non-atopic patients.[7] In a proof-of-concept study in non-atopic asthma patients, treatment with omalizumab resulted – as per in atopic patients – in a significant reduction of high-affinity IgE receptor (FcεRI) expression on blood basophils and plasmacytoid dendritic cells (pDC2), which hampered IgE binding and the subsequent production on proinflammatory mediators.[8] Additionally, omalizumab treatment was associated with an increase in FEV_1 with a positive trend in some relevant clinical endpoints, such as asthma exacerbations.[8] In another proof-of-concept trial, omalizumab therapy (but not placebo) reduced IgE expression and IgE sensitization of target cells within the bronchial mucosa, and increased FEV_1 versus baseline despite withdrawal of conventional therapy.[9] Interestingly, it has been hypothesized that patients labelled as 'non-allergic' might in fact have a localized allergy to an unrecognized allergen, with elevated concentrations of allergen-specific IgE antibodies in the airways.[7]

Our study has several limitations. Its single-arm retrospective nature relies on the accuracy and completeness of the information entered into the clinical records. This has especially affected predictors of response such as FeNO and the level of eosinophils, which were not routinely assessed in the clinical practice at the time of the study. The benefits of omalizumab presented here are those observed in the population of non-atopic patients who achieved disease control after one year of treatment with omalizumab. It is unknown how many other patients classified as non-atopic in the clinical practice did not benefit from this treatment.

In summary, in the population of patients with non-atopic severe asthma who achieved full disease control after one year of treatment with omalizumab, the clinical and pulmonary benefits were remarkable and similar to those described for atopic patients. A reduction in the use of healthcare resources was also documented. Large randomized controlled trials are warranted to confirm the value of omalizumab in this population of patients.

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Conflicts Of Interest

The authors declare that they have no conflicts of interest.

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Table 1. Demographic, anthropometric, clinical characteristics and asthma history of non-atopic asthma patients of FENOMA study

Variable	**N=80**
Age, years, mean (SD)	58.7 (12.2)
Sex, female, n (%)	52 (65.0)
Smoking status, n (%) Never smoked Former ([?]1 year) Time since having quit smoking, years, mean (SD) Current smoker Packages/year, mean (SD)	61 (76.2) 13 (16.2) 11.7 (5.1) 6 (7.5) 21.5 (21.3)
Asthma history in the year before starting treatment with omalizumab	**Asthma history in the year before starting treatment with omalizumab**

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Time since diagnosis of: Asthma, years, median (Q1;Q3) Severe persistent asthma, years, median (Q1;Q3)	12.9 (8.3; 23.3) 5.7 (4.4; 7.8)
Daytime symptoms, n (%)[a] No symptoms or symptoms [?]2 times a week >2 times a week Daily symptoms Continuous symptoms (several times a day)	3 (3.7) 15 (18.7) 43 (53.8) 18 (22.5)
Night-time symptoms, n (%)[b] No symptoms [?]2 times a month >2 times a month > 1 time a week Frequents	7 (8.9) 9 (11.4) 12 (15.2) 25 (31.6) 25 (31.6)
Need for rescue medication, n (%)[a] No or [?]2 days a week >2 days a week (but not every day) Every day Several times a day	6 (7.6) 22 (27.8) 41 (51.9) 10 (12.6)
Pulmonary function, median (Q1;Q3)[a] FEV_1, %	69.0 (58.0; 79.0)
Non-severe asthma episodes, median (Q1;Q3)	5.0 (3.0; 8.0)
Severe or clinically significant exacerbations in the previous year, median (Q1;Q3)[a]	3.0 (2.0; 5.0)
Use of healthcare resources due to severe or clinically significant exacerbations, mean (SD) Visits to emergency units[b] Hospital admissions No. days of hospital stay[c] Intensive care units admission No. days of intensive care units stay[d]	3.0 (2.8) 1.0 (1.9) 6.8 (3.2) 0.2 (0.6) 5.4 (3.9)
Background treatments for asthma, n (%) ICS Dose, µg, median (Q1; Q3) OCS[e] Dose, mg, median (Q1; Q3)	80 (100.0) 800 (640,0; 1,000.0) 54 (67.5) 25.0 (6.0; 50.0)
IgE levels, IU/mL, median (Q1;Q3)	187.50 (106,0; 399,0)

[a]n=79; [b]n=78;[c]n=27; [d]n=7

FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

Percentages are given for valid population

Table 2. Non-severe exacerbations, pulmonary function and use of healthcare resources / absenteeism before and after one year of treatment with omalizumab (n=80)

Variables	**Before treatment**	**After treatment**	**P-value***
Non-severe exacerbations, median (Q1; Q3) Change	5.0 (3.0; 8.0)[a]	1.0 (0.0; 2.0) -4.0 (-8.0; 2.0)	<0.0001
Pulmonary function (FEV_1%), median (Q1; Q3) Change	69.0 (58.0;79.0)[b]	86.0 (80.0; 94.0)[c] 15.0 (5.0; 27.0)	<0.0001

Variables	Before treatment	After treatment	P-value*
Use of healthcare resources / absenteeism due to non-severe exacerbations, median (Q1; Q3) Unplanned visits to primary care Unplanned visits to specialists School or workplace absenteeism, days	5.0 (3.0; 8.0)[d] 2.0 (0.0; 4.0)[c] 2.0 (0.0; 15.0)[e]	0.0 (0.0; 1.0)[b] 0.0 (0.0; 0.5) 0.0 (0.0; 0.0)[f]	- - <0.0001

[a]n=74; [b]n=79;[c]n=78; [d]n=72;[e]n=63; [f]n=69.

*Wilcoxon signed-rank test.

FEV_1, forced expiratory volume in 1 second.