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

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 $\geq 50\%$ 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 asthma³. 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 also patients with non-atopic asthma.⁴⁻⁵

The observational, multicenter, retrospective, real-life FENOMA study specifically evaluated patients who achieved improved asthma control after one year of treatment with omalizumab.⁶ The study included 345 patients, 80 (23.2%) of whom had non-atopic asthma, as defined by a negative skin prick test. 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.⁶

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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 improved 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 [FEV₁]), v) number of non-severe exacerbations and vi) use of healthcare resources, i.e. unplanned visits to primary care or specialists and vii) 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 blood eosinophil count and exhaled nitric oxide fraction (FeNO) before and after treatment.

Demographic, clinical characteristics and asthma history (before starting treatment with omalizumab, baseline phenotypes are for 1-year pre-treatment period) are shown in **Table 1**. Mean (standard deviation [SD]) age of patients was 58.7 (12.2) years and 65% were female. Before treatment, 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 (75.92%) 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 the patients (53.7%, n=43) needed no rescue medication. Median FEV₁ 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. The proportion of patients receiving ICS decreased from 100.0% to 91.2% (**Table 2**). The dose of ICS was reduced in 61.2% (n=49) patients and maintained in 35% (n=28). Daily dose also decreased from a median (Q1; Q3) of 800.0 (640.0; 1000.0) µg to 600.0 (400.0; 1000.0) µg (difference = -240 [-500.0; 0.00] µg). This difference was not statistically significant (P=0.8668). Relative blood eosinophil count was available in 68 (85.0%) patients before treatment and in 53 (66.2%) after one-year treatment. Median (Q1; Q3) was 5.5% (3.0; 8.0) and 4.0% (2.0; 7.0), respectively (change: -1.0 [-4.0; 0.0]) (**Table 2**). FeNO levels were available in 37 patients (46.2%) before treatment and in 39 (48.7%) after one-year treatment. Median (Q1; Q3) was 33.0 (20.0; 49.0) ppb and 21.0 (12.0; 33.0) ppb, respectively (change: -10.0 [-28.0; 0.0]) (**Table 2**).

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.⁷ However, this series is the most extensive study in patients with non-atopic asthma in Spain published to date, and provides data on improved disease control. There have been several potential suggestions to explain the effectiveness of omalizumab in non-atopic patients.⁸ In a proof-of-concept study in non-atopic asthma patients, treatment with omalizumab resulted – as 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.⁹ Additionally, omalizumab treatment was associated with an increase in FEV₁ with a positive trend in some relevant clinical endpoints, such as asthma exacerbations.⁷ 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 FEV₁ versus baseline despite withdrawal of conventional therapy.¹⁰ 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.⁸

This 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.

This series is the most extensive study in Spanish patients with non-atopic asthma responders to omalizumab achieving control of the disease published to date. 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 improved 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

PC received personal fees from Novartis as advisory board member of FENOMA study. **AM** is full-time employee and reports personal fees from Novartis Farmacéutica, S.A, outside the submitted work. **SQ** reports personal fees and non-financial support from GSK, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Novartis, personal fees and non-financial support from Mundipharma, personal fees and non-financial support from Teva, personal fees and non-financial support from Allergy Therapeutics, outside the submitted work. **EMM** reports personal fees from AstraZeneca, personal fees from Boehringer-Ingelheim, personal fees from Chiesi, personal fees from GlaxoSmithKline, personal fees from Novartis, personal fees from Mundipharma, personal fees from ALK, personal fees from TEVA, personal fees from Pfizer, outside the submitted work. **AM** reports non-financial support from Novartis, during the conduct of the study; personal fees from GSK, personal fees from Esteve, personal fees from Ferrer, personal fees from Novartis, personal fees from Rovi, outside the submitted work. **ID** reports non-financial support from Novartis, during the conduct of the study; personal fees from Novartis, personal fees from Sanofi, personal fees from GSK, personal fees from ASTRA-ZENECA, personal fees from LETI, grants and personal fees from THERMOFISHER, personal fees from ALK, personal fees from STALLERGENES, personal fees from DIATER, personal fees from CHIESI, personal fees from INMUNOTEK, outside the submitted work. **GSC** reports non-financial support from Novartis, during the conduct of the study; personal fees from Astrazeneca, personal fees from Boehringer, personal fees from

Novartis, personal fees from GSK, personal fees from Chiesi, personal fees from Bial, personal fees from Menarini, outside the submitted work. **APG** have no conflict of interest.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this Letter to the Editor. All authors contributed to the interpretation of the data and the writing and reviewing of all drafts of the Letter to the Editor. All authors approved the final version to be published, and agree to be accountable for all aspects of this work

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Table 1. Baseline 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)
Body Mass Index, kg/m ² , mean (SD) ^a	28.26 (5.09)
Smoking status, n (%)	
Never smoked	61 (76.2)
Former (≥1 year)	13 (16.2)
Time since having quit smoking, years, mean (SD)	11.7 (5.1)
Current smoker	6 (7.5)
Packages/year, mean (SD)	21.5 (21.3)
Asthma history in the year before starting treatment with omalizumab	
Time since diagnosis of:	
Asthma, years, median (min; max; Q1;Q3)	12.9 (3.3; 54.8; 8.3; 23.3)
Severe persistent asthma, years, median (min; max; Q1;Q3)	5.7 (2.1; 35.8; 4.4; 7.8)
Daytime symptoms, n (%) ^b	
No symptoms or symptoms ≤2 times a week	3 (3.7)
>2 times a week	15 (18.7)
Daily symptoms	43 (53.8)
Continuous symptoms (several times a day)	18 (22.5)
Night-time symptoms, n (%) ^c	
No symptoms	7 (8.9)
≤2 times a month	9 (11.4)

>2 times a month	12 (15.2)
> 1 time a week	25 (31.6)
Frequents	25 (31.6)
Need for rescue medication, n (%) ^a	
No or ≤2 days a week	6 (7.6)
>2 days a week (but not every day)	22 (27.8)
Every day	41 (51.9)
Several times a day	10 (12.6)
Severe or clinically significant exacerbations in the previous year, median (min; max; Q1;Q3) ^b	3.0 (0.0; 10.0; 2.0; 5.0)
Use of healthcare resources due to severe or clinically significant exacerbations, mean (SD)	
Visits to emergency units ^c	3.0 (2.8)
Hospital admissions	1.0 (1.9)
No. days of hospital stay ^d	6.8 (3.2)
Intensive care units admission	0.2 (0.6)
No. days of intensive care units stay ^e	5.4 (3.9)
IgE levels, IU/mL, median (min; max; Q1;Q3)	187.50 (2.0; 2327.0; 106,0; 399,0)

Main comorbidities, n (%)	
Allergic rhinitis	21 (26.25)
Nasal polyposis	31 (38.75)
Chronic sinusitis	17 (21.25)
Atopic dermatitis	2 (2.50)

^an=77; ^bn=79; ^cn=78; ^dn=27; ^en=7

Continuous variables are presented as median and quartile 1 (Q1) and 3 (Q3), as applicable.

FEV₁, 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 (min; max; Q1; Q3)	5.0 (0.0; 52.0; 3.0; 8.0) ^a	1.0 (0.0; 18.0; 0.0; 2.0)	
Change, median (Q1; Q3)		-4.0 (-8.0; 2.0)	<0.0001
Pulmonary function (FEV ₁ %), median (min; max; Q1; Q3)	69.0 (35.0; 128.0; 58.0; 79.0) ^b	86.0 (41.0; 143.0; 80.0; 94.0) ^c	
Change, median (Q1; Q3)		15.0 (5.0; 27.0)	<0.0001
Use of healthcare resources / absenteeism due to non-severe exacerbations, median (min; max; Q1; Q3)			
Unplanned visits to primary care	5.0 (0.0; 30.0; 3.0; 8.0) ^d	0.0 (0.0; 15.0; 0.0; 1.0) ^b	<0.0001
Unplanned visits to specialists	2.0 (0.0; 8.0; 0.0; 4.0) ^c	0.0 (0.0; 5.0; 0.0; 0.5)	<0.0001
School or workplace absenteeism, days	2.0 (0.0; 365.0; 0.0; 15.0) ^e	0.0 (0.0; 25.0; 0.0; 0.0) ^f	<0.0001
Relative blood eosinophil count, median (min; max; Q1; Q3)	5.5 (0.0; 24.0; 3.0; 8.0) ^g	4.0 (0.0; 17.0; 2.0; 7.0) ^h	
Change, median (Q1; Q3)		-1.0 (-4.0; 0.0)	0.003
FeNO levels (ppb), median (min; max; Q1; Q3)	33.0 (8.0; 99.0; 20.0; 49.0) ⁱ	21.0 (8.0; 82.0; 12.0; 33.0) ^j	
Change, median (Q1; Q3)		-10.0 (-28.0; 0.0)	0.0006
Background treatments for asthma, n (%)			
ICS	80 (100.0)	73 (91.2)	
OCS	54 (67.5)	13 (10.4)	
Asthma Control Test (ACT), median (min; max; Q1; Q3)	13.00 [6.00, 22.00]	22.00 (12.00; 25.00; 18.00; 24.00) ^k	

Q3)	19.00;10.00; 15.00) ^k	20.00; 24.00) ^l	
Change, median (Q1; Q3)		9.00 (6.00; 13.00)	<0.0001

^an=74; ^bn=79; ^cn=78; ^dn=72; ^en=63; ^fn=69; ^gn=68; ^hn=53; ⁱn=37; ^jn=39; ^kn=25; ^ln=34

*Wilcoxon signed-rank test. Percentages are given for valid population

FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; OCS, oral corticosteroids.