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Factors reducing omalizumab response in severe asthma

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ABSTRACT

Background: Despite adding Omalizumab to conventional therapy, several severe asthmatics still show poor disease control. We investigated the factors that may affect a reduced Omalizumab response in a large population of severe asthmatics.

Methods: 340 patients were retrospectively evaluated. FEV_1%, FVC%, Asthma Control Test (ACT), fractional exhaled nitric oxide (FENO), possible step-downs/step-ups of concomitant therapies, exacerbations, disease control levels, ICS doses and SABA use, observed at the end of treatment, were considered as a response to Omalizumab.

Results: Age was an independent risk factor for a reduced response concerning FEV_1%, FVC%, ACT and for a lower asthma control. Obesity (vs normal weight) was a determinant condition for exacerbations (OR:3.114[1.509–6.424], $p = 0.002$), for a disease partial/no control (OR:2.665[1.064–6.680], $p = 0.036$), for excessive SABA use (OR:4.448[1.837–10.768], $p = 0.002$) and for an unchanged/increased level of concomitant asthma medications. Furthermore, obesity also reduced the response in FEV_1 ($\beta = -6.981$,$p = 0.04$), FVC ($\beta = -11.689$,$p = 0.014$) and ACT ($\beta = -2.585$, $p = 0.027$) and was associated with a higher FENO level ($\beta = 49.045$,$p = 0.040$). Having at least one comorbidity was a risk factor for exacerbations (OR:1.383[1.128–1.697], $p = 0.008$) and for an ACT < 20 (OR:2.410[1.071–3.690], $p = 0.008$). Specifically, chronic heart disease was associated with both a lower ACT and FVC% whereas gastroesophageal reflux with a partial/no asthma control. Nasal polyps were a predisposing factor leading both to exacerbations and to the use of higher inhaled corticosteroids doses. Moreover, smoking habits, pollen or dog/cat dander co-sensitizations may negatively influence Omalizumab response.

Conclusion: Age, obesity, comorbidities, smoking habits, nasal polyps, allergic poly-sensitization might reduce Omalizumab effectiveness independently to other asthma-influencing factors.

1. Introduction

Severe asthma is a disease phenotype requiring high-intensity treatment to obtain disease control [1]. However, low asthma control (i.e. a greater emergency department visits, hospitalizations and excessive short-acting β_2-agonist and/or prednisolone use) characterizes a large part of subjects affected by "severe" asthma. In fact, despite using high doses of inhaled corticosteroids (ICS), long acting bronchodilators and anti-leukotrienes, optimal asthma control may not be achieved in most patients affected by 'severe' asthma. In case of severe persistent uncontrolled asthma, caused by perennial allergens (mainly dust mite), guidelines recommend adding Omalizumab, a humanized recombinant DNA-derived monoclonal antibody [1]. It inhibits the interaction between IgE and the two main IgE receptors FcεRI and CD23/FcεRII

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FcεRI, thus preventing mast cell and basophil activation and blocking IgE binding to CD23 on B-cells and antigen-presenting cells [2]. Practically, Omalizumab, specifically in real-life studies, has achieved a better asthma control by reducing daily corticosteroid dosages, exacerbations, hospitalizations and emergency department visits [3–7]. However, a high percentage (34%) of 'severe' asthmatics, although treated with Omalizumab, may show a poor disease control [5]. It is totally unclear which factors may negatively affect Omalizumab response. According to some authors [5,7], comorbidities (namely, obesity, gastro-oesophageal reflux disease, chronic rhinosinusitis, nasal polyps and mental disorders) and age are associated with the lack of asthma control and persistence of frequent disease exacerbations in severe asthmatics even though treated with Omalizumab. On the contrary, according to others [6], Omalizumab response in participants with comorbidities (rhinitis, obesity and cardiovascular diseases) was similar to the response in patients affected just by asthma. However, such results were obtained without adjusting for confounding factors like age, weight, therapy, blood eosinophils, age of asthma onset, aspirin intolerance, infections and others. The above said factors characterize several asthma phenotypes that may show a different response to treatment.

Therefore, aim of this study was to evaluate the possible factors that may influence Omalizumab effectiveness in a large population of severe asthmatics in a real-life setting, considering a large number of confounding clinical/biological factors that may cause a treatment interference.

2. Materials and methods

We retrospectively analyzed 340 severe asthmatics who had already been recruited for two of our previous studies [5,6,8]. All patients were severe allergic asthmatics poorly controlled despite a treatment with high doses of ICS plus long-acting bronchodilators, sometimes also associated with anti-leukotrienes, for which it was necessary to add Omalizumab, as recommended by steps 5 of asthma GINA guidelines [1]. All patients were under Omalizumab treatment for different periods of time (from 4 to 120 months). Lung function variables (FEV_1%, FVC%), Asthma Control Test (ACT), fractional exhaled nitric oxide (FENO), number of moderate/severe exacerbations, disease control, ICS doses, SABA use as rescue medication and possible variations in the use of other concomitant therapies (step-downs/step-ups), observed at the end of each patient's treatment period, were considered as responses to anti-IgE therapy. Asthma control levels were assessed by following GINA guidelines criteria [1]. Each patient's allergies had been established by prick tests to various aero-allergens. ACT ≥ 20 and FENO ≤ 25 ppb were considered normality cut-offs (good asthma control and low airway inflammation). Moderate/severe exacerbations requiring systemic corticosteroids for at least 3 days and/or hospitalizations were taken into account. Obesity Class I, II and III were defined by a BMI of 30–35, 35–40 and > 40 respectively. The daily dosage of beclomethasone dipropionate or equivalent dose for other corticosteroids used (fluticasone budesonide or others) was expressed as low (≤ 500 mg), medium (500–1000 mg) or high (≥ 1000 mg), according to GINA classification of ICS dose equivalence [1]. SABA use (number of times a week) during the 30 days before the end of each patient's treatment period with Omalizumab was also taken into account. As regards comorbidities, only those which had documented evidence were considered.

2.1. Statistical analysis

Our analysis was affected by using multivariate logistic and linear regression models. The tested variables (evaluated at the end of each patient's period of Omalizumab treatment) were the following: ACT < 20 vs > 20; FENO > 25 ppb vs < 25 ppb, no/partial asthma control vs good control, stable/increased therapy levels vs reduced treatments, persistent high/unchanged dosages of ICS vs reduced ICS doses and SABA use ≥ once a week vs no SABA use. For the above said binary dependent variables (considered as the response of Omalizumab therapy), a stepwise multivariate logistic regression model was applied to test the relationship with several factors: sex, age, smoking habits, asthma familiarity, BMI (underweight, overweight, obesity class I [BMI = 30–35], II [BMI = 35–40], and III [BMI > 40]), various allergen sensitizations, IgE values, blood eosinophils, aspirin intolerance, infection recurrence, hypertension, diabetes, rhino-sinusitis, polyposis, chronic heart disease, osteoporosis, gastroesophageal reflux, COPD, mental disorders, age of asthma onset, Omalizumab treatment duration, daily doses of ICS, the use of Montelukast, oral corticosteroids and nasal steroids. For each continuous dependent variable (FEV_1%, FVC%, FENO, ACT), measured at the end of each patient's period of Omalizumab treatment, a stepwise multivariate linear regression model was applied to test the relationship with all the above listed covariates.

Table 1
Characteristics of 340 severe asthmatics treated with Omalizumab.

Age	53 [44–63]
Sex M/F	121/219 (35.6/64.4%)
Smokers	81 (24%)
Ex-smokers	23 (6.8%)
Pack/year	10 [5–20]
Smokers of < 10 pack/year	32 (9.5%)
Smokers of > 10 pack/year	29 (8.6%)
Age of asthma onset (yrs)	29 [15–40]
Family history with asthma	131 (45.6%)
House dust mite sensitization	276 (85.7%)
Pollen sensitizations	198 (63.5%)
Mould sensitizations	42 (13.5%)
Cat/dog dander sensitizations	90 (28.4%)
Mono-sensitized (to 1 allergen)	120 (37.3%)
Poly-sensitized (≥2 allergens)	202 (62.7%)
FEV_1% pre-Omalizumab[a]	74 [60–87]
FEV_1/FVC pre-Omalizumab[a]	71 [59–79.6]
Total serum IgE UI/ml	314.5 [167.5–553.5]
Blood eosinophils n/mm3[b]	270 [92–430]
FENO (ppb)[c]	25 [16–40]
N° of subjects with Eosinophils > 3%[b]	113 (63.5%)
N° of subjects with rhinitis	224 (66.7%)
N° of subjects with sinusitis	117 (35.8%)
N° of subjects with nasal polyposis	78 (23.5%)
N° of subjects with hypertension	53 (22.5%)
N° of subjects with chronic heart disease	16 (6.8%)
N° of subjects with diabetes	8 (3.4%)
N° of subjects with osteoporosis	14 (5.9%)
N° of subjects with gastro-esophageal reflux	116 (35.3%)
N° of subjects with OSAS	9 (3.9%)
N° of subjects with mental disorders	24 (8.5%)
BMI	26.48 [23.98–29.40]
N° of subjects with underweight	7 (2.1%)
N° of subjects with normal weight	110 (32.4%)
N° of subjects with overweight	146 (42.9%)
N° of subjects with obesity class I	51 (15%)
N° of subjects with obesity class II	21 (6.2%)
N° of subjects with obesity class III	5 (1.5%)
N° of subjects with 0 comorbidity	107 (31.8%)
N° of subjects with 1 > comorbidity	233 (68.2%)
N° subjects with aspirin intolerance	62 (21.9%)
Monthly omalizumab dose (mg)	450 [300–600]
Months of omalizumab treatment	32 [17–50]
Patients in treatment with ICS	340 (100%)
Patients in treatment with LABA	300 (89%)
Patients in treatment with montelukast	195 (60.7%)
Patients in treatment with tiotropium	42 (13%)
Patients in treatment with theophilline	29 (10.9%)
Patients in treatment with oral corticosteroids	23 (8.4%)
Nasal steroids	114 (41.3%)

[a] Evaluated on 125 patients where values were collected before starting Omalizumab
[b] evaluated on 178 patients;
[c] evaluated on 135 subjects