

RESEARCH LETTER

Asthma with multiple allergic comorbidities is associated with complete response to omalizumab

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To the Editor

Patients with severe asthma constitute a heterogeneous population and different phenotypes have been identified both in adults and children.¹ Severe asthma affects 4.5% of children with current asthma. Several studies have shown that omalizumab, a humanized anti-IgE monoclonal antibody, is effective in exacerbations and asthma control and well tolerated in children with severe allergic asthma.² However, as biotherapy response varies among patients, it is important to clearly define which children will benefit the most from treatment. We conducted a study to define predictive markers of response to omalizumab in children with severe allergic asthma, with the hypothesis that early and complete response (CR) corresponds to a specific phenotype. The children were selected from the Severe Asthma Molecular Phenotype cohort, a prospective monocentric cohort of severe asthmatic children included from January 2011 to December 2015 in a paediatric tertiary centre for the treatment of asthma and allergies, in Paris.³ Among the patients included in the cohort we selected children aged from 6 to 18 years (a) with severe asthma and/or steroid-refractory asthma (defined as per GINA recommendations [www.ginasthma.org]) (b) who were sensitized to a perennial allergen (c) and who had received omalizumab administered subcutaneously at the recommended dose for at least 4 months. Severe asthma was defined as controlled asthma with high-dose inhaled corticosteroid (ICS) (500 mg or more of equivalent fluticasone propionate (FP) per day) and two other controller

medications; steroid-refractory asthma was defined as uncontrolled asthma despite high-dose ICS (≥ 500 mcg/d FP) and two other controller medications. All included patients also benefited from repeated individual or group health education measures during this time to improve compliance to anti-asthmatic treatment and received advice by an environmental specialist to reduce exposure to indoor biological pollutants. The following baseline parameters were collected: gender, age, body mass index, parents' socio-economic status, tobacco smoke exposure, maternal and paternal asthma, age at wheeze onset, Asthma Control Test (ACT), severe exacerbation, eczema, allergic rhinitis, IgE-mediated food allergy, blood eosinophilia, fractional exhaled nitric oxide (FeNO), total-IgE level, multiple sensitization (≥ 2 allergic sensitizations⁴) and lung function. The children who were reported as having eczema in our study had a high score on the SCORing Atopic Dermatitis (SCORAD) index at least once in the year prior to the introduction of omalizumab. The SCORAD index is defined by Kunz et al.⁵ We defined baseline exacerbation as the number of severe exacerbations treated by oral corticosteroids or requiring hospitalization in the year before assessment for omalizumab treatment. The response to omalizumab was evaluated at 4 months of treatment by ACT score, lung function and the number of severe exacerbations. A decrease in the number of exacerbations was defined as: either no exacerbations or a decrease in the number of exacerbations by more than 50% during omalizumab treatment. No response (NR) was defined as: (a) uncontrolled asthma

TABLE 1 Asthma characteristics and omalizumab response according to cluster analysis

	Patient characteristics, n = 45	Cluster 1 Eosinophilic asthma with abnormal lung function and poor response to omalizumab, n = 16	Cluster 2 Uncontrolled asthma with tobacco smoke exposure, normal lung function and inconstant response to omalizumab, n = 11	Cluster 3 Severe asthma with multiple allergic comorbidities with mostly normal lung function and constant response to omalizumab, n = 18	P value*
Gender, male n (%)	32 (71)	10 (63)	6 (55)	16 (89)	0.076
Age, mo, mean $\pm$ SD	1 $\pm$ 3	13 $\pm$ 3	13 $\pm$ 3	12 $\pm$ 3	0.57
BMI, mean $\pm$ SD	20 $\pm$ 6	20 $\pm$ 5	21	20	0.58
Low socio-economic categories of parents, n (%)	21 (47)	10 (63)	3 (27)	8 (44)	0.191
Tobacco exposure, n (%)	11 (24)	1 (6)	6 (55)	4 (22)	0.016*
Maternal asthma, n (%)	10 (22)	0 (0)	6 (55)	4 (22)	0.002*
Paternal asthma, n (%)	12 (27)	4 (25)	3 (27)	5 (28)	0.03*
Fluticasone, μ g/d, mean $\pm$ SD	797 (262)	819 (256)	855 (250)	742 (279)	0.497
FEV ₁ % of predicted value, mean $\pm$ SD	75 $\pm$ 3	65 $\pm$ 10	81 $\pm$ 20	79 $\pm$ 13	0.006*
Eczema, n (%)	15 (33)	1 (6)	1 (9)	13 (72)	<0.001*
IgE-mediated food allergy, n (%)	14 (31)	3 (19)	2 (18)	9 (50)	0.086
Allergic rhinitis, n (%)	42 (93)	15 (94)	10 (91)	17 (94)	1.000
Total-IgE, mean $\pm$ SD	1226 $\pm$ 1595	792 $\pm$ 514	802 $\pm$ 1364	1871 $\pm$ 2127	0.084
Multiple sensitization, n (%)	27 (57)	9 (56)	3 (27)	15 (83)	0.009*
Eosinophilia $\geq$ 300/mm ³ , n (%)	35 (78)	15 (94)	4 (36)	16 (89)	0.001*
FeNO $\geq$ 21 ppb, n (%)	36 (80)	16 (100)	5 (46)	15 (83)	0.001*
CR, n (%)	21 (47)	1 (6)	4 (36)	16 (89)	<0.001*

BMI, body mass index; FEV₁, forced expiratory volume; FeNO, exhaled nitric oxide; CR, complete response to omalizumab.

* $P < 0.05$.

(ACT score <20) and (b) no decrease in number of severe exacerbations and (c) no improvement of lung function values (FEV₁, and/or FEV₁/FVC). Partial response (PR) was defined as one or two following parameters: (a) total asthma control with an ACT score >20, (b) a decrease in number of exacerbation (c) normalization or unchanged lung function values (FEV₁ $\geq$ 95%, and/or FEV₁/FVC $\geq$ 85%). CR was defined as improvement of all parameters.

The objective of the study was to define predictive markers of a CR to omalizumab at 4 months by logistic regression and cluster analysis. For multivariate analysis we applied a step-by-step analysis that allowed us to choose the best model from parameters selected by univariate analysis ($P < 0.20$) and data from literature. Cluster analysis included the baseline parameters described above.

Of the 45 children included (average age 12.6 ($\pm$ 2.7) years), 21 (47%) were evaluated as being in CR, 20 (44%) in PR and four (9%) in NR. The mean concentration of fluticasone was 796.7 [$\pm$ 262] μ g per day (Table 1). For three children (7%), the daily treatment contained oral steroids. The median length of follow-up was 119 days (IQR: 36 days). In the step-by-step multivariate analysis the selected

variables from univariate analysis and literature were eczema, allergic rhinitis, IgE-mediated food allergy, multiple sensitization ($\geq$ 2 allergic sensitizations), blood eosinophilia and total-IgE level. The best logistic regression model revealed that eczema adjusted for multiple sensitization was predictive of CR at 4 months (compared to PR and NR), OR 5.71 (CI 95% [1.43-27.83], $P = 0.02$). Cluster analysis identified three independent clusters: Cluster 1 consisted of 16 children with eosinophilic asthma (eosinophilia $>300/\text{mm}^3$ $n = 15$ (94%), $P = 0.001$), abnormal lung function (mean FEV₁ 65 $\pm$ 10 of predicted value $P = 0.006$) and poor response to omalizumab ($n = 1$ (6%), $P < 0.001$ with CR); Cluster 2 of 11 children with tobacco smoke exposure ($n = 6$ (55%), $P = 0.016$), normal lung function and inconstant response to omalizumab ($n = 4$ (37%) with CR); and Cluster 3 of 18 children with multiple allergic comorbidities ($n = 15$ (83.3%), $P = 0.001$) and especially eczema ($n = 13$ (72%), $P < 0.001$), multiple sensitization ($n = 15$ (83%) $P < 0.009$), mostly normal lung function and CR to omalizumab ($n = 16$ (89%), $P < 0.001$ with CR) (Table 1).

The strength of the study is that it was performed in a well-defined population of children with severe allergic asthma in a

real-life setting and stringent criteria were applied to establish CR. However, it was a single-centre study and the proportion of NR was low, possibly reflecting inclusion bias. Some of the children had very high IgE levels for omalizumab prescription. Nevertheless, after eliminating a hyper-IgE syndrome (within an immune deficiency), this is the case for many children with severe allergic asthma as reported in a French omalizumab register published by Deschildre et al.⁶ Multivariate analysis indicated that eczema was a predictive factor of CR to omalizumab. To the best of our knowledge, no other study has shown this association. Nevertheless, various case series report clinical improvement of eczema under treatment with omalizumab, particularly in children.⁷ Univariate analysis did not identify a high FeNO (>21 ppb) or high blood eosinophil count (>300/mm³) as being associated with early response to omalizumab. This result is in accordance with STELLAIR conclusions.⁸ However, in Cluster 3, characterized by the highest prevalence of CR to omalizumab (89% of the children), most had blood eosinophil levels above 300/mm³ (89%), FeNO values >21 ppb (83%), but also multiple sensitization (83%). In their real-life study, Deschildre et al.⁷ found that the majority of children had a good response to omalizumab at 1 year and were characterized by more than three allergic sensitizations (66% of cases) and high IgE levels (mean 1125 kU/L). Moreover, in adults with severe allergic asthma, the EXTRA study reported that some T2 related biomarkers, such as high levels of exhaled nitric oxide (FeNO), elevated blood eosinophil counts and high serum periostin levels, were predictive markers of omalizumab response especially in terms of reducing exacerbations.⁹ The new finding of our study is that, while eosinophilic driven biomarkers are necessary, they are not sufficient to ensure a CR to omalizumab: conversely to Cluster 1, with the statistically highest level of eosinophilic driven biomarkers and poor response to omalizumab, Cluster 3 had high eosinophilic driven biomarkers as well as multiple allergic comorbidities and multiple sensitization and the best response to omalizumab (89%). This suggests that the presence of multiple allergic comorbidities and multiple sensitizations are necessary to ensure a CR to omalizumab. Cluster 3 is comparable to a severe asthma phenotype described by various teams: multiple allergic comorbidities and high eosinophilic driven biomarkers (high total serum IgE level (median, 733 kU/L) and blood eosinophil count (median, 400 cells/mm³)).^{3,10} Overall then, omalizumab would appear to target the T2 inflammatory process, especially when linked to allergy.

This study thus demonstrates by two statistical approaches that while eosinophilic driven biomarkers are necessary, they are not sufficient to ensure a CR to omalizumab and that multiple

allergic comorbidities and multiple sensitization with normal lung function, is the phenotype associated with early and CR to omalizumab.

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REFERENCES

1. Fitzpatrick AM, Teague WG, Meyers DA, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol*. 2011;127(2):382-389.e1-13.
2. Chipps BE, Lanier B, Milgrom H, et al. Omalizumab in children with uncontrolled allergic asthma: review of clinical trial and real-world experience. *J Allergy Clin Immunol*. 2017;139(5):1431-1444.
3. Guiddir T, Saint-Pierre P, Purenne-Denis E, et al. Neutrophilic steroid-refractory recurrent wheeze and eosinophilic steroid-refractory asthma in children. *J Allergy Clin Immunol Pract*. 2017;5(5):1351-1361.e2.
4. Gabet S, Just J, Couderc R, Bousquet J, Seta N, Momas I. Early polysensitization is associated with allergic multimorbidity in PARIS birth cohort infants. *Pediatr Allergy Immunol*. 2016;27(8):831-837.
5. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1997;195(1):10-19.
6. Deschildre A, Marguet C, Salleron J, et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J*. 2013;42(5):1224-1233.
7. Holm JG, Agner T, Sand C, Thomsen SF. Omalizumab for atopic dermatitis: case series and a systematic review of the literature. *Int J Dermatol*. 2017;56(1):18-26.
8. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M; STELLAIR investigators. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. *Eur Respir J*. 2018;51(5):1702523.
9. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804-811.
10. Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. *Eur Respir J*. 2012;40(1):55-60.

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