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Early View

Original article

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Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study

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Abstract

Omalizumab is a monoclonal anti-immunoglobulin E antibody used to treat severe allergic asthma (SAA). The aim of the STELLAIR study was to determine the importance of pre-treatment blood eosinophil count (EOS) as a predictive measure for response to omalizumab. This retrospective real-life study was conducted in France between December 2015 and September 2016 using medical records of SAA omalizumab-treated patients. Response to omalizumab was assessed by three criteria: physician evaluation, reduction of ≥40% in annual exacerbation rate, and combination of both. Response rate was calculated according to blood EOS count measured in the year prior to omalizumab initiation. 872 SAA omalizumab-treated patients were included by 78 physicians (723 adults and 149 minors aged 6-17 years). EOS was ≥300/µl in 52.1% of adults and 73.8% of minors. By physician evaluation, 67.2% of adults and 77.2% of minors were responders and 71.1% adults and 78.5% minors had a 40% reduction in exacerbation rate. In adults, response rate for combined criteria was 58.4% (95% CI 53.2-63.4) in EOS ≥300 (n=377) and 58.1% (95% CI 52.7-63.4) in EOS <300 (n=346). This study shows that a large proportion of patients with SAA have EOS ≥300 and suggests that omalizumab effectiveness is similar in *high* and *low* EOS subgroups.

Take-home message

Omalizumab is a treatment option for severe allergic asthma irrespective of blood eosinophil count

Funding

Novartis Pharmaceuticals

Keywords:

Allergy; Asthma; Eosinophils; Omalizumab; Real-world; Severe asthma

Abbreviations

BTS = British Thoracic Society

EOS = Eosinophil count

CR = Combined Response

GETE = Global Evaluation of Treatment Effectiveness

GINA = Global Initiative for Asthma

ICS = Inhaled Corticosteroids

LABA = Long Acting Beta Agonist

OCS = Oral Corticosteroids

SAA = Severe allergic asthma

SEA = Severe eosinophilic asthma

Introduction

Severe asthma is a heterogeneous disease with several phenotypes including allergic and eosinophilic asthma.[1,2] About 70% of asthmatic patients are allergic.[3] Allergens that enter the airway are presented to T lymphocytes by dendritic cells which initiate the cell-mediated immune response, particularly the maturation and migration of type 2 T helper cells (Th2). Th2 cells stimulate B cells to produce immunoglobulin E (IgE) antibodies as well as stimulate secretion of proallergic cytokines, such as interleukins (IL)-4, -5, -9, and -13. IL-4 is essential for the production of IgE, whereas IL-5 is involved in the recruitment of eosinophils and basophils, which then promote inflammation.

A humanized anti-IgE monoclonal antibody, omalizumab, indicated as an add-on therapy for children (from the age of 6 years) and adults with uncontrolled persistent severe allergic asthma (SAA), was first introduced in Europe in 2005.[4,5] Omalizumab has been shown to prevent exacerbations, improve symptoms, quality of life and to decrease systemic corticosteroid use both in large-scale randomized studies,[6–8] and 'real-life' studies.[9–15]

Novel therapies which target IL-5 or its receptor in the same Th2 pathway are emerging for the treatment of severe eosinophilic asthma.[16] The clinical benefits of these therapies are more pronounced in patients with a high blood eosinophil count (EOS) and their indication is consequently restricted to adults with refractory severe eosinophilic asthma (SEA) defined by a blood EOS ≥300 cells/µL over 12 months.[16] Interestingly, a large proportion of patients with SAA also have blood EOS ≥300 cells/µL.[17]

The aim of the STELLAIR [Next Steps Toward personalized care: EvaLuating responders to XoLAIR® treatment in patients with severe allergic asthma] study was to determine the importance of pre-treatment blood EOS as a predictive measure for response to omalizumab.

Methods

Study design and participants

This multi-center, non-interventional, retrospective, observational study was performed in France from December 21st 2015 to September 30th 2016 using data from medical records of patients with SAA treated with omalizumab. Hospital-based pulmonologists and pediatric pulmonologists with experience in treating severe asthma were asked to provide data of all their consecutive patients meeting the STELLAIR inclusion criteria. Physicians could include consecutive patients meeting inclusion criteria up to a maximum of 30 patients per physician. STELLAIR is a retrospective non-interventional study, which does not require registration on clinicaltrials.gov. This real-life study was approved by the institutional committees in charge of data-protection in biomedical research in France (*Comité Consultatif sur le Traitement de l'Information en matière de Recherche, Commission Nationale de l'Informatique et des Libertés*).

Inclusion criteria were any patient: ≥6 years of age; who had been treated with omalizumab for poorly controlled SAA; with a documented blood EOS measurement taken within 12 months prior to omalizumab treatment initiation; with the number of exacerbations recorded during the 12 months prior to omalizumab initiation; and who had a documented physician evaluation of response to omalizumab after 4 to 6 months of treatment and number of exacerbations recorded. Patients that refused collection of their medical data for research purposes were excluded in accordance with the ethics committee requirements.

Investigators entered patient data in an electronic case report form (e-CRF) and extracted for four time points: T_{-12} corresponding to the 12 months prior to omalizumab initiation; T_0 corresponding to time of omalizumab treatment initiation; T_{4-6} corresponding to first effectiveness assessment after at least 4 months of treatment (as required in omalizumab summary of product characteristics); and T_{12} corresponding to effectiveness assessment at 12 months following treatment initiation (12-month effectiveness evaluation for renewal of prescription; if available). The study being retrospective, T_{4-6} and T_{12} (if available) were prior to the study start in December 2015.

Outcomes

The primary outcome was response to omalizumab treatment at $T_{4\text{-}6}$ compared with $T_{\text{-}12}$ using three criteria:

- The physician's overall evaluation according to the Global Evaluation of Treatment Effectiveness (GETE) scale. GETE is a five-point scale, where 1=excellent (complete control of asthma), 2=good (marked improvement), 3=moderate (discernible, but limited improvement), 4=poor (no appreciable change) and 5=worsening. The rating of symptoms control as 'excellent'/'good', or 'moderate'/'poor'/'worsening' allowed the patient to be respectively defined as a 'responder', or 'non-responder'.
- A decrease in the annual exacerbation rate with a 'responder' defined as having a reduction in the annual exacerbation rate of at least 40%. An asthma exacerbation was defined as a significant worsening of asthma requiring a short burst of oral corticosteroids (OCS) or, for patients treated with an OCS, an increase in the OCS dose regimen. The annual exacerbation rate was calculated by adjusting the number of exacerbations according to the duration of exposure to omalizumab treatment; treatment duration was 4–6 months for all patients and 12 months for 706 patients (81%).
- A combination of the GETE evaluation and a 40% reduction in the annual exacerbation rate (Combined Response (CR)).

Response was analyzed according to blood EOS cells/µL measured in the year prior to omalizumab initiation (last measurement available prior to initiation).

Statistical analysis

Statistical analysis was performed using SAS software (version 9.4, SAS Institute, North Carolina USA). Descriptive analyses of qualitative variables were expressed as number of patients for each category and percentage. Quantitative variables were presented as means and standard deviation ($\pm$SD) for normally distributed variables or as the medians and interquartile (Q1-Q3) ranges when not. The 95% confidence intervals were indicated for each of the three outcome endpoints. The number of missing values were reported for each variable, where indicated. All statistical tests were two-sided and the alpha risk was set at 5%.

Role of the funding source

The funder of the study contributed to the study design, data interpretation, and writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Of the 510 physicians who were invited to participate, 102 accepted and 80 sites were finally opened; of these, 78 (62 pulmonologists and 16 pediatric pulmonologists) actively recruited a total of 879 patients who met the eligibility criteria. 872 of these patients, of whom 723 (83%) were adults and 149 (17%) were aged 6 to 17 years (minors) were included in the study (Figure 1). Seven patients, all ≥18 years of age, were excluded from analysis due to incomplete medical records at T_{4-6} (n=5) or because there was no documentation of other asthma controller treatments (n=2).

Most of the patients (n=804, 92.2%) were still treated with omalizumab after the first effectiveness assessment at T_{4-6}, and 81% (n=706) had a follow-up at T_{12}, i.e. 12 months after omalizumab initiation.

Patient characteristics are presented in Table 1. For adults and minors, omalizumab was prescribed as an add-on therapy to improve asthma control in patients who had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids (ICS), plus a long-acting beta$_2$-agonist (LABA) with or without OCS treatment. At T_0, more than a third of the adult patients (n=243, 34.4%) were treated with OCS maintenance treatment (at a mean daily dose of 20.4 mg/day).

All the patients included in this study had uncontrolled SAA, as reflected by the number of asthma events in the previous 12 months: exacerbations (5.2 [$\pm$3.9] minors; 4.3 [$\pm$3.1] adults) and frequent unplanned hospitalizations (79 [53%] minors; 295 [40.8%] adults). Exacerbations and hospitalizations in the 12 months prior to omalizumab by blood EOS in minors and adults are shown in Table 2.

In minors, this severe allergic population was characterised by very high total IgE levels (median IgE level of 850 IU/mL). In adults, the median total serum IgE level was 285 IU/mL.

The median blood EOS_{T-12} was more than twice as high in minors compared with adults (619 cells/µL vs 308 cells/µL) (Table 3). The distribution of EOS_{T-12} ranged from 0 to ≥1000 cells/µL and was on average higher in minors than adults. A total of 52.1 % (n=377) of adult SAA patients had a blood EOS ≥300 cells/µL.

Omalizumab effectiveness was first evaluated at T_{4-6} by the treating pulmonologist or pediatrician using the GETE scale after a median of 154 days of treatment: 77.2% minors (n=115) and 67.2% adults (n=486) were reported to be responders (i.e. excellent=complete control or good=marked improvement of asthma) to omalizumab (Figure 2).

During the treatment period, between T_0 and $T_{4-6,}$ 34.9% minors (n=52) and 43% adults (n=311) had presented at least one exacerbation. The mean number of exacerbations in patients with at least one exacerbation was 1.9 in minors and 1.8 in adults. The mean decrease in the annual exacerbation rate was 60.2% in minors (±88.8) and 48.5% (±93.5) in adults. Most of the patients were classified as responders according to the reduction in the annual exacerbation rate (reduction of at least 40%): 78.5% in minors (95% CI 71.1–84.8) and 71.1% in adults (95% CI 67.6–74.4).

CR to omalizumab treatment (combination of GETE and the exacerbation rate) was reached in 67.8% (95% CI 59.7–75.2) and 58.2% (95% CI 54.5–61.8) of minor and adult patients, respectively.

Among the 723 adults, 377 had blood EOS ≥300 cells/µL and 346 <300 cells/µL. In adults, the GETE response, 40% reduction of exacerbation response and CR rates to omalizumab treatment were similar irrespective of the EOS count, using a cut-off of either 300 cells/µL or 150 cells/µL (Figure 3). Moreover, the proportion of CR was similar in 'low EOS' (<300 cells/µL), and 'high EOS' (≥300 cells/µL) in the whole adult population (Figure 4).

The percentage reduction in asthma exacerbation in patients with blood EOS below or above 300 cells/µL and IgE levels below or above 75 IU/mL are shown in Figure 5 and indicate that omalizumab was effective in all these patient subgroups.

In minors (n=149), 110 had EOS ≥300 cells/µL and 39 <300 cells/µL. Responders to omalizumab were also analyzed using a 600 cells/µL cut-off. This cut-off was the median EOS_{T-12} in this subgroup and allowed a better distribution of the population: 80 patients ≥600 cells/µL and 69 patients <600 cells/µL. CR to omalizumab treatment was 70.9% (95% CI 61.5–79.2) in minors with an EOS ≥300 cells/µL (n=110) and 59% (95% CI 42.1–74.4) in those with an EOS <300 cells/µL (n=39). With a 600 cells/µL cut-off, CR reached 72.5% (95% CI 61.4–81.9) in EOS ≥600 cells/µL (n=80) and 62.3% (95% CI 49.8–73.7) in EOS <600 cells/µL (n=69).

All in all, the response rate was similar for adults and minors, irrespective of studied EOS cut-offs and for all definitions of response (Table 4).

At $T_{12,}$ data for treatment effectiveness (including number of exacerbations, hospitalizations and modification in OCS therapy) were available for 706 of the study participants, with 577 adults and 129 minors completing 373 and 403 days of omalizumab therapy, respectively. The results were adjusted on a mean duration of 12 months. Half of the minors (46/92) and 61.9% (179/289) of the adults experienced at least one exacerbation during the 12 months of treatment (mean ± SD 1.1 ± 1.6 and 1.4 ± 2, respectively). Compared with the 12-month pre-treatment period, the exacerbation rates were reduced by 70.4% ± 50 in minors and 58.6% $\pm$ 67.8% in adults. A total of 20/129 (15.5%) minors and 63/577 (10.9%) adults were hospitalized at least once during the 12 months of treatment (mean 0.2 ± 0.6 and 0.2 $\pm$ 0.6, respectively). The annual rate of hospitalizations was on average the same in minors and adults (mean 0.2 $\pm$ 0.6). Compared to the 12 months pre-treatment period, the mean reduction in hospitalization rates was 73.2% in minors and 72.6% in adults.

A total of 243 adults were treated with OCS (average daily dose of 20.4 mg/day) at T_0. 195 patients (80.2%) with OCS as maintenance treatment at T_0 had a follow-up visit available at T_{12}. At $T_{12,}$ 96 (49.2%) of these patients had completely discontinued OCS therapy. Among those who were still treated with an OCS, a majority (62.1%) had decreased their median daily dose by 10 mg/day (interquartile range: 5–15 mg/day), which represented a median reduction in daily OCS dose of 50% (interquartile range 40–70%). Omalizumab effectiveness (GETE, number of exacerbations and modification in OCS therapy) in adults with OCS as maintenance treatment was observed in patients with EOS <300 cells/µL and ≥300 cells/µL (data not shown).

Information on blood EOS_{T12} was available for 212 patients (173 adults and 39 minors). According to the GETE scale, excellent responder adult patients (n=35) showed a 45.5% median decrease in EOS while good (n=88) and non-responders (n=48) had a median decrease only of 20.1% and 0%, respectively. Similar results were observed with minors with 55.7% and 53.3% decrease in excellent (n=11) and good (n=17) responders while non-responders (n=10) presented a decrease of 11.4%. These results suggest a decrease of the EOS count when SAA patients respond to omalizumab. The change was not statistically correlated to response status (ANOVA).

Sixty-eight children (50 males, 74%) were in the 6–12-year-old age group (mean age 8.6 ± 1.7 years at omalizumab initiation). The median blood EOS was 776 cells/µL and EOS was ≥300 cells/µL in 74% of cases. Omalizumab effectiveness evaluated at $T_{4\text{-}6}$ by the treating pulmonologist or pediatrician using the GETE scale was excellent or good in 80.9% of cases (95% CI 69.5–89.4%). It was 73.7% (95% CI 48.8–90.9%]) if EOS was <300 cells/µL and 83.7% (95% CI 70.3–92.7%) if EOS was ≥300 cells/µL. The yearly rate of asthma exacerbations decreased from 5.7 [±3.3] prior to omalizumab therapy to 1.4 [±3.3] at $T_{4\text{-}6}$. CR to omalizumab treatment (combination of GETE and the exacerbation rate) was reached in 75% of cases (95% CI 63.0–84.7), 68.4% (43.5–87.4%) if EOS was <300 cells/µL and 77.6% (63.4–88.2%) if EOS was ≥300 cells/µL.

Sixty-four patients were current smokers, and 180 were former smokers (18.0 ± 13.4 pack years). There was a trend for reduced effectiveness in current and former smokers versus nonsmokers. CR to omalizumab treatment (combination of GETE and the exacerbation rate) was reached in 48.4% of current smokers (95% CI 36.2–60.7), 55.6% of former smokers (95% CI 48.3–62.81), and 61.2% of nonsmokers (95% CI 56.7–65.8). When EOS was <300 cells/µL, CR was reached in 42.5% of current smokers (95% CI 27.2–57.8), 56.8% of former smokers (95% CI 46.5–67.2), and 62.0% of nonsmokers (95% CI 55.3–68.7).

Discussion

This report suggests that omalizumab response in patients with SAA does not vary with EOS: omalizumab appears to be as effective in patients with "high" EOS (≥300 cells/µL) as in those with "low" EOS (<300 cells/µL). These results remain similar with all other blood EOS cut-offs studied and for all definitions of response.

These real-life findings confirm those already published in the omalizumab arm of EXTRA study post-hoc analysis that showed similar exacerbation rates during the 48-week omalizumab treatment period in low-EOS (<260 cells/µl at baseline) and high-EOS (≥260 cells/µl at baseline) subgroups, respectively 0.65 and 0.70.[18] However, the reduction in exacerbation rate seen with omalizumab (versus placebo) was lower in patients with low- versus high-eosinophil count at baseline;[18] a possible explanation for this difference could be the high exacerbation rate in the high-eosinophil count group treated with placebo.[18] Similarly, in a post-hoc analysis of the INNOVATE study, omalizumab produced a greater reduction in exacerbation rate in patients with higher versus lower baseline EOS,[19] and a recent post-hoc analysis of two clinical studies has also shown a greater reduction in exacerbation rate with omalizumab in patients with higher vs lower EOS.[20] In the latter study, only 3% of patients had been hospitalized for an exacerbation in the previous year suggesting that patient had moderate to severe asthma, while a 45% reduction in exacerbation rate with omalizumab in patients with a low EOS at baseline showed clinical effectiveness even with low EOS.[20] Possible explanations for the differences seen between these post-hoc analyses and our study include STELLAIR being a real-life study rather than a randomized, controlled clinical trial, STELLAIR was not a post-hoc analysis, and the patient population here had more severe asthma. Irrespective of this, what is clear from the STELLAIR study and the other post-hoc analyses published to date is that omalizumab is effective at reducing the exacerbation rate of patients with SAA, and while some studies have demonstrated a greater response in patients with higher baseline EOS, this does not rule out the effectiveness of omalizumab treatment.

The STELLAIR study provides new data regarding the distribution of EOS in SAA patients before starting GINA step 5 therapies (add-on with either tiotropium, anti-IgE or anti-IL-5 therapies). The study shows different mean EOS for adults (451 cells/µL) and minors (685

cells/µL) in the 12 months prior to omalizumab initiation. 73.8% of minors and 52.1% of adults had EOS ≥300 cells/µL. Such adults could be eligible to anti-IL5 therapies. This figure could be underestimated since a number of patients were treated by OCS. In a post-hoc analysis of the INNOVATE clinical trial,[19] 59% (245 patients) of the [12-75] year-old patients had EOS ≥300 cells/µL at baseline. Similar results were found in a post-hoc analysis of the EXTRA trial with 52% of patients having a median baseline EOS ≥260 cells/µL.[18] The proportions of patients with SAA and EOS ≥300 cells/µL are close for these three studies that assessed patients with severe asthma eligible for biotherapy. A cut-off of 400 cells/µL has also been used in several publications focusing on EOS in asthmatic patients whatever the severity;[21,22] these studies showed a prevalence rate of 18–26% of patients with EOS ≥400 cells/µL. A recent large UK cohort of 130 000 asthmatic patients found a proportion of 16% patients with EOS >400 cells/µL and 26% in severe patients (step 4 and 5 according to the British Thoracic Society therapy steps).[23] In our study, 40% of adults had EOS ≥400 cells/µL at baseline. Taken together, these findings show that there is considerable overlap between SAA and SEA patients, both corresponding to type 2 (Th2 high) asthma.

The main limitation of the study resides in its retrospective design. However, the patient characteristics and omalizumab effectiveness are similar to the results of previous studies conducted during the clinical development,[6–8] and in real-life settings,[9–15] both for adults and minors. The STELLAIR study confirms the differences between severe asthma in adults and in minors: adults are more frequently female (60.9%) whereas minor patients are more often male (63.1%). Selection bias was also reduced by asking all participating investigators to include consecutive patients corresponding to strict selection criteria. Bias was addressed in part by the e-CRF which was developed to minimize missing data using appropriate controls, particularly for endpoints with mandatory fields. Data check and review confirmed that patients were effectively eligible for omalizumab and very few patients (n=7) were excluded from the analysis. Furthermore, to ensure the robustness of the results, response to omalizumab was defined by three sets of criteria which completely converged. Finally, the STELLAIR study is the largest real-world omalizumab study conducted in France, including more than 10% of all omalizumab-treated SAA patients in the country. Taken together, it is likely that these results can be generalized to SAA patients eligible for omalizumab and managed by pulmonologists and pediatricians in France.

Although various biologic therapies with different mechanisms of action targeting each of the phenotypes exist or are under development, deciding who is best treated with which therapy is a challenging task[24]. Given the considerable overlap in SAA and SEA, physicians have to decide which therapeutic strategy will be more effective for a patient presenting SAA and SEA. The STELLAIR study results suggest that, conversely to antibodies targeting specifically the eosinophil activation pathway, omalizumab therapy is effective in eligible patients with SAA irrespective of the pre-treatment blood EOS. These findings deserve to be further investigated by prospective studies assessing the clinical effectiveness of biologics targeting overlapping populations of patients with severe persistent allergic asthma and a high blood EOS.

Contributors

MH, MM, LM, VLG contributed to data acquisition, and data analysis and interpretation. MH, MM contributed to the study concept, design, analysis, and interpretation. CT and JJ contributed to analysis and interpretation. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

Declaration of interests

MH has relationships with drug companies including AstraZeneca, GSK, Novartis, Roche, Sanofi/Regeneron and TEVA. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards.

MM reports personal fees from Novartis Pharma SAS, GSK, Boehringer Ingelheim, personal fees from University of Bordeaux, during the conduct of the study; grants from Novartis Pharma, outside the submitted work.

CT reports personal fees from Kappa Santé, during the conduct of the study; personal fees and other from AstraZeneca, personal fees and other from Boeringher, personal fees from Chiesi, grants, personal fees and other from GSK, personal fees and other from Novartis, personal fees from Teva, personal fees and other from ALK, other from Sanofi, outside the submitted work.

LM and VLG are employees at Novartis Pharmaceuticals.

JJ reports personal fees from ALK, STALLERGENE, grants and personal fees from NOVARTIS, outside the submitted work.

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Table 1. Demographics and clinical characteristics by age group at T_0, date of omalizumab (OMA) initiation.

	Age Group		
	Minors (6-17 years) (n=149)	**Adults (≥ 18 years) (n=723)**	**Total (n=872)**
Sex			
Male	94 (63·1%)	283 (39·1%)	377 (43·2%)
Female	55 (36·9%)	440 (60·9%)	495 (56·8%)
Age at OMA initiation (years)	11·4 (3·1)	50.8 (14·2)	44.1 (19·7)
Weight (kg)	45·6 (18·1)	75·1 (16·8)	70 (20·3)
Smoking status			
Non-smoker	142 (97·9%)	441 (64·4%)	583 (70·2%)
Former smoker	0 (0%)	180 (26·3%)	180 (21·7%)
Current smoker	3 (2·1%)	64 (9·3%)	67 (8·1%)
Missing	4 -	38 -	42 -
If former/ current smoker, number of pack-years	1 (.)	18 (13·4)	17.9 (13·5)
Missing	2	50	52
Any comorbidity	136 (91·3%)	595 (82·3%)	731 (83·8%)
Conjunctivitis	31 (22·8%)	85 (14·3%)	116 (15·9%)
Nasal polyps	0 (0%)	165 (27·7%)	165 (22·6%)
Perennial rhinitis	108 (79·4%)	300 (50·4%)	408 (55·8%)
Seasonal rhinitis	55 (40·4%)	106 (17·8%)	161 (22·0%)
Sinusitis	5 (3·7%)	100 (16·8%)	105 (14·4%)
Urticaria	5 (3·7%)	25 (4·2%)	30 (4·1%)
Atopic dermatitis	50 (36·8%)	40 (6·7%)	90 (12·3%)
Food allergy	37 (27·2%)	40 (6·7%)	77 (10·5%)
Angioedema	1 (0·7%)	2 (0·3%)	3 (0·4%)
Anaphylaxis	4 (2·9%)	4 (0·7%)	8 (1·1%)
Aspirin or NSAID hypersensitivity	0 (0%)	57 (9·6%)	57 (7·8%)
Depression/Anxiety	7 (5·1%)	88 (14·8%)	95 (13%)
Obesity	12 (8·8%)	121 (20·3%)	133 (18·2%)
GERD	15 (11%)	169 (28·4%)	184 (25·2%)
Asthma therapy at OMA initiation			
ICS	149 (100%)	708 (98·2%)	857 (98·5%)
LABA	123 (83.1%)	687 (95·4%)	810 (93·3%)
OCS	3 (2·1%)	243 (34·4%)	246 (28·9%)
Daily dose of OCS (mg/day)	17·5 (17·7)	20·4 (14·2)	20·3 (14·2)
Daily dose of ICS (beclomethasone equivalent, µg/day)	1 545 (± 615.2)	1 990.8 (± 1200)	1 914.7 (± 1134)
Number of hospitalizations in the 12 months prior	2·3 (1·9)	1·7 (1·4)	1·9 (1·5)
Number of exacerbations in the 12 months prior	5·2 (3·9)	4·3 (3·1)	4·5 (3·2)
Total serum IgE (IU/mL)			
Mean (SD)	1361 (1439)	528·6 (798)	676 (996)
Median (IQR)	850·5 (353·5 - 1881·5)	285 (110 - 602)	345 (126 - 718)
Range	22 - 8700	2 - 6900	2 – 8700
Blood EOS count in 12 months prior (cells/µL)			
Mean (SD)	684·6 (507·6)	450·6 (600·4)	490·6 (591·9)
Median (IQR)	619 (280 – 930)	308 (166 – 560)	340 (175 - 622.5)
Range	0 - 2640	0 - 8885	0 – 8885

Data presented as means (SD) or n (%) unless specified otherwise. Minors include patients aged 6-17 years of age; Adults ≥ 18 years of age. T_0= study initiation; NSAID=non-steroidal anti-inflammatory drug; GERD= Gastroesophageal reflux disease; OMA=omalizumab; ICS= inhaled corticosteroid; LABA= Long-acting β adrenoceptor agonists; OCS=oral corticosteroid.

Table 2: Exacerbations and hospitalizations before omalizumab initiation by blood eosinophil counts (EOS) measured in the year prior to omalizumab initiation in 149 minors (6-17 years) and 723 adults (≥18 years).

		EOS_{T-12}					
		< 300 cells/µL		≥ 300 cells/µL		TOTAL	
		Minors	Adults	Minors	Adults	Minors	Adults
		N=39	N=346	N=110	N=377	N=149	N=723
Number of exacerbations		5.1 (± 3.3)	4.2 (± 3.2)	5.2 (± 4.1)	4.4 (± 3)	5.2 (± 3.9)	4.3 (± 3.1)
	95% CI	[4.1-6.2]	[3.9-4.6]	[4.4-6.0]	[4.1-4.7]	[4.6-5.8]	[4.1-4.6]
Number of hospitalizations		2.1 (± 1.7)	1.8 (± 1.6)	2.4 (± 2.1)	1.7 (± 1.1)	2.3 (± 1.9)	1.7 (± 1.4)
	95% CI	[1.5-2.8]	[1.6-2.1]	[1.8-2.9]	[1.5-1.8]	[1.9-2.7]	[1.6-1.9]

Minor patients include ages 6-17 years; Adult patients include ages >18 years.

Table 3. Distribution of EOS counts measured in the 12 months prior to omalizumab (OMA) initiation by age group

	Minors (6-17 years) (n=149)	Adults (≥18 years) (n=723)	Total (n=872)
Delay from CBC to OMA initiation (months)	2·8 (2·8)	3·1 (3)	3 (2·9)
OCS maintenance treatment at the CBC			
Yes	5 (3·4%)	216 (30·9%)	221 (26·2%)
No	141 (96·6%)	483 (69·1%)	624 (73·8%)
Missing	3 -	24 -	27 -
EOS counts (cells/µL)			
<150	17 (11·4%)	163 (22·5%)	180 (20·6%)
≥ 150	132 (88·5%)	560 (77·5%)	692 (79·4%)
≥ 300	110 (73·8%)	377 (52·1%)	487 (55·8%)
≥ 400	98 (65·8%)	291 (40·2%)	389 (44·6%)
≥ 500	87 (58·4%)	221 (30·6%)	308 (35·3%)
≥ 1000	32 (21·5%)	56 (7·7%)	88 (10·1%)

CBC = Cell Blood Count; EOS= blood eosinophil counts; OMA= omalizumab; OCS= oral corticosteroid. Minors include patients aged 6-17 years of age; Adults ≥ 18 years of age.

Table 4. Primary endpoints at T_{4-6}, by blood eosinophil counts (EOS) measured in the year prior to omalizumab (OMA) initiation in 149 minors (6-17 years) and 723 adults (≥18 years).

	EOS_{T-12}					
	< 300 cells/µL		≥ 300 cells/µL		Total	
	Minors	Adults	Minors	Adults	Minors	Adults
Primary Endpoints at T_1	**N=39**	**N=346**	**N=110**	**N=377**	**N=149**	**N=723**
1. GETE score						
Responder, n (%)	25 (64·1%)	231 (66·8%)	90 (81·8%)	255 (67·6%)	115 (77·2%)	486 (67·2%)
95% CI	[47·2–78·8]	[61·5–71·7]	[73·3–88·5]	[62·7–72·3]	[69·6–83·7]	[63·7–70·6]
2. Reduction in the annual exacerbation rate						
Mean number of exacerbations between T_0-T_{4-6} (±SD)	1·6 (± 1·3)	1·7 (± 1·1)	2·1 (± 1·6)	1·8 (± 1·3)	1·9 (± 1·5)	1·8 (± 1·2)
Mean annual rate change, % (±SD)	-64·7 (± 67·5)	-52·5 (± 89·6)	-58·6 (± 95·4)	-44·9 (± 97)	-60.2 (± 88·8)	-48.5 (± 93·5)
Responder with a 40 % reduction in the annual exacerbation rate, n (%)	31 (79·5%)	250 (72·3%)	86 (78·2%)	264 (70·0%)	117 (78·5%)	514 (71·1%)
95% CI	[63·5–90·7]	[67·2–76·9]	[69·3–85·5]	[65·1–74·6]	[71·1–84·8]	[67·6–74·4]
3. Combination						
Combined Responder, n (%)	23 (59·0%)	201 (58·1%)	78 (70·9%)	220 (58·4%)	101 (67·8%)	421 (58·2%)
95% CI	[42·1–74·4]	[52·7–63·4]	[61·5–79·2]	[53·2–63·4]	[59·7–75·2]	[54·5–61·8]

The primary endpoints at T_{4-6} include: 1) The physician's overall evaluation (GETE scale for symptoms control): Responders include: Excellent responders (complete control of asthma) and Good responders (marked improvement). Data not presented for Non-responders (discernible, no appreciable change or worsening). 2) A decrease in the yearly rate of exacerbations with omalizumab: a responder has at least a reduction of 40% in the yearly occurrence of exacerbations before and after omalizumab initiation. 3) The combination of both definitions (physician's evaluation and exacerbation rate decrease). Data are mean (SD) or n (%) unless specified otherwise. Minor patients include ages 6-17 years; Adult patients include ages >18 years.

Figure 1: Flow chart

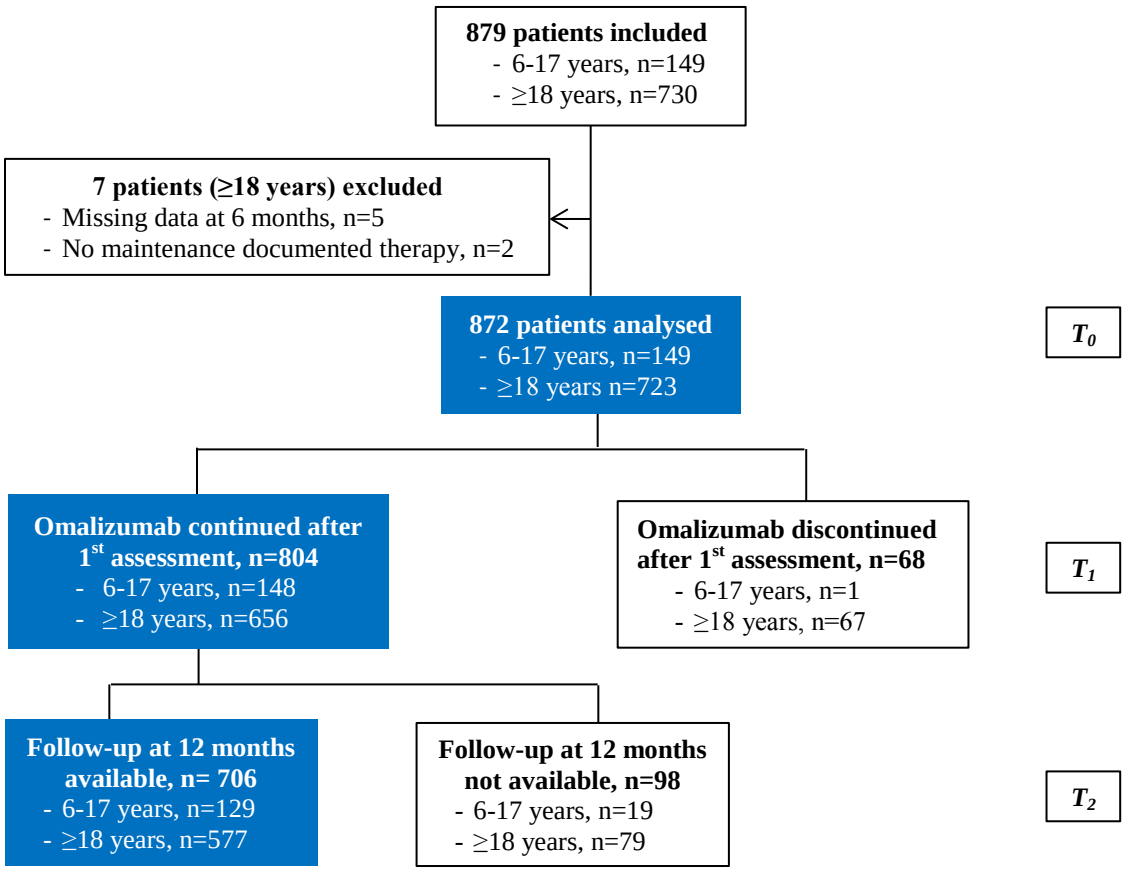


Figure 2: Global evaluation of treatment effectiveness at $T_{1,}$ by age group

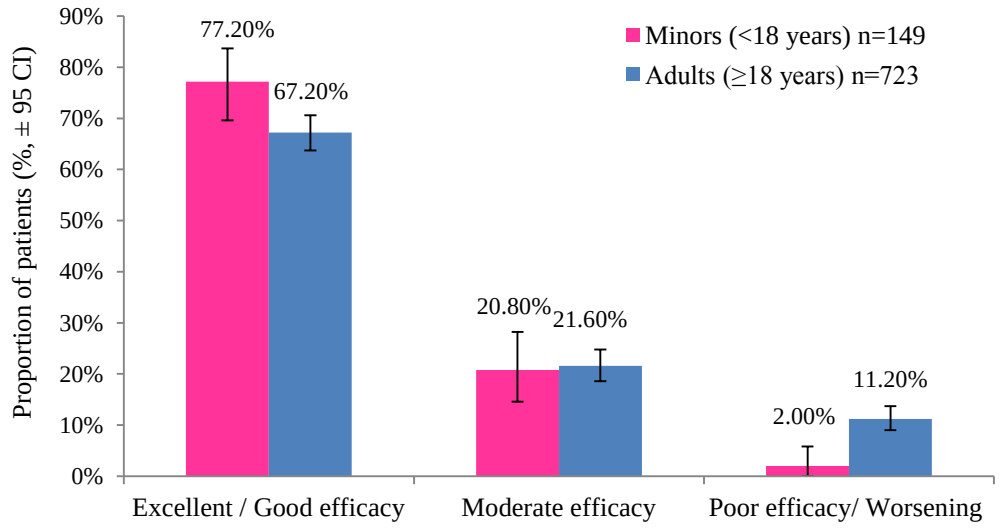
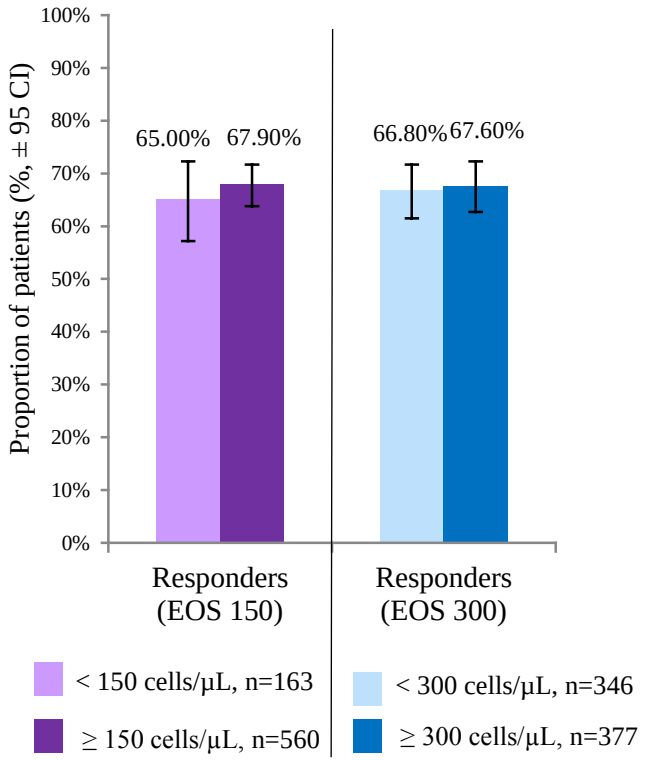
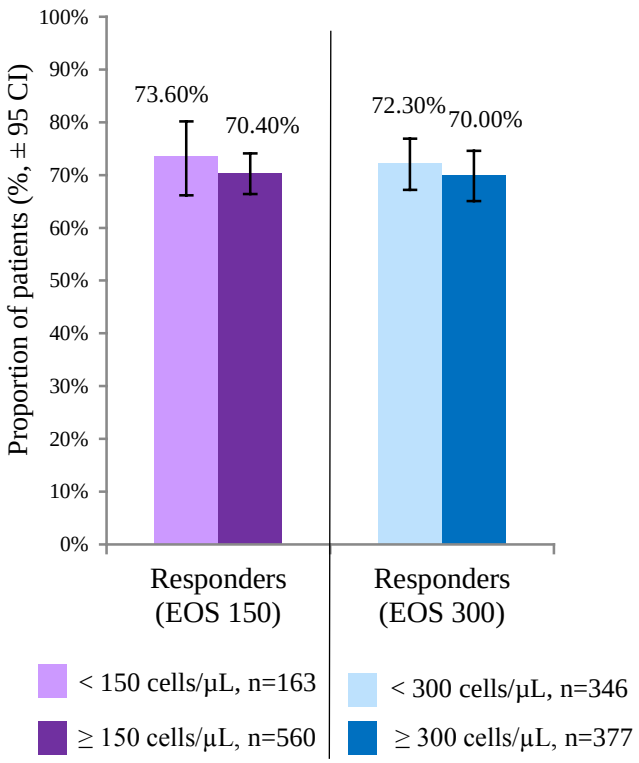


Figure 3: Responders to omalizumab treatment in adult patients at T_1 according to blood eosinophil cut-off at 150 cells/µL and 300 cells/µL

A – Responders based on physician's global evaluation (GETE)



B – Responders based on 40% decrease in the annual exacerbation rate



C – Combined Responders (GETE + exacerbations)

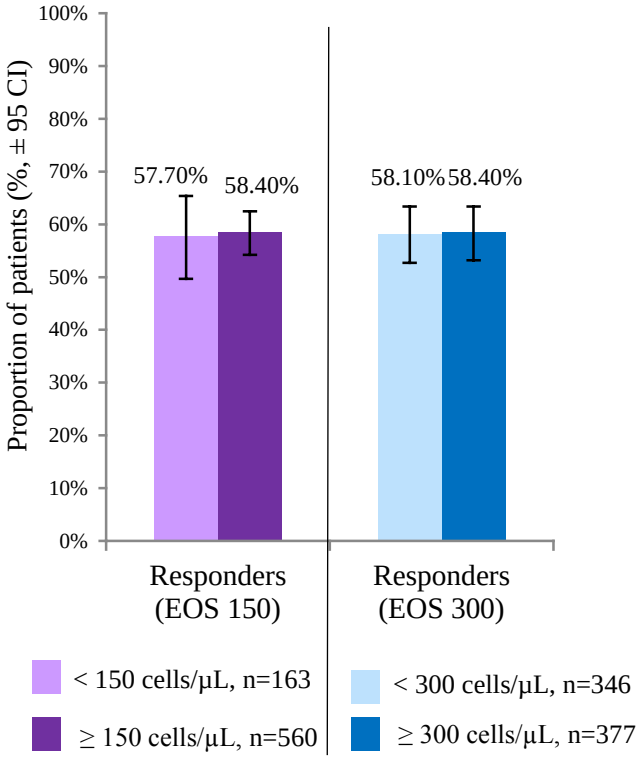


Figure 4: Combined Responders to omalizumab treatment in adults according to the distribution of blood eosinophil count in the whole population

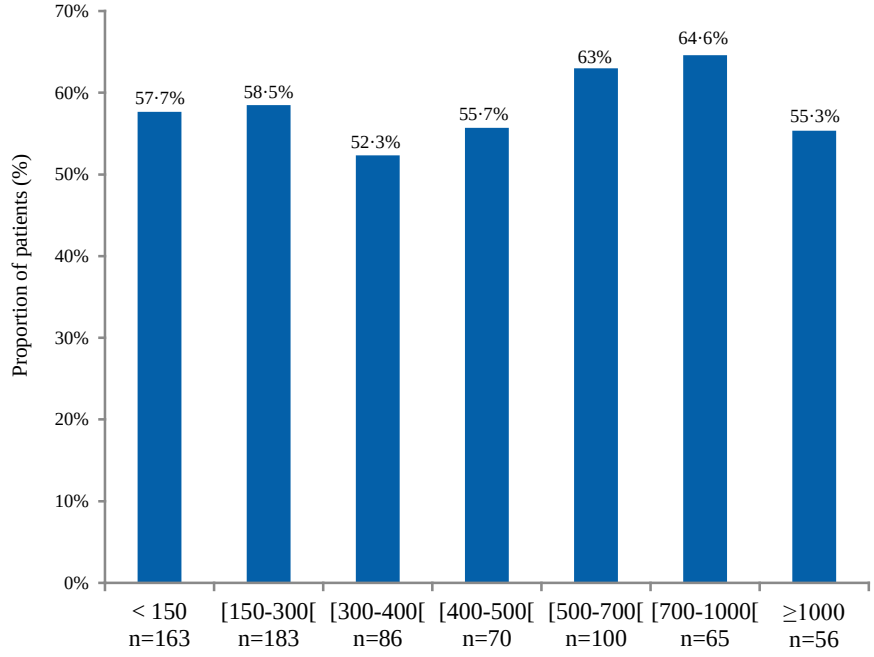


Figure 5: Reduction in asthma exacerbation rate according to blood eosinophil count (EOS) and serum IgE in adult patients with severe allergic asthma