



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

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Omalizumab is a treatment option for severe allergic asthma irrespective of blood eosinophil count
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ABSTRACT Omalizumab is a monoclonal anti-IgE 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 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 $\geq 40\%$ in annual exacerbation rate and a combination of both. Response rate was calculated according to blood eosinophil count measured in the year prior to omalizumab initiation.

872 SAA omalizumab-treated patients were included by 78 physicians (723 adults (age ≥ 18 years) and 149 minors (age 6–17 years)). Blood eosinophil count was ≥ 300 cells- μL^{-1} 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 $\geq 40\%$ reduction in the exacerbation rate. In adults, the response rate for combined criteria was 58.4% (95% CI 53.2–63.4%) for blood eosinophils ≥ 300 cells- μL^{-1} (n=377) and 58.1% (95% CI 52.7–63.4%) for blood eosinophils < 300 cells- μL^{-1} (n=346).

This study shows that a large proportion of patients with SAA have a blood eosinophil count ≥ 300 cells- μL^{-1} , and suggests that omalizumab effectiveness is similar in “high” and “low” eosinophil subgroups.

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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 that 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 IgE antibodies as well as stimulate secretion of pro-allergic 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 humanised 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, to improve symptoms and quality of life, and to decrease systemic corticosteroid use both in large-scale randomised studies [6–8] and “real-life” studies [9–15].

Novel therapies that target IL-5 or its receptor in the same Th2 pathway are emerging for the treatment of severe eosinophilic asthma (SEA) [16]. The clinical benefits of these therapies are more pronounced in patients with a high blood eosinophil count and their indication is consequently restricted to adults with refractory SEA defined by a blood eosinophil count ≥ 300 cells· μL^{-1} over 12 months [16]. Interestingly, a large proportion of patients with SAA also have a blood eosinophil count ≥ 300 cells· μL^{-1} [17].

The aim of the STELLAIR (Next Steps Toward personalised care: EvaLuating responders to XoLAIR treatment in patients with SAA) study was to determine the importance of pre-treatment blood eosinophil count as a predictive measure for response to omalizumab.

Methods

Study design and participants

This multicentre, noninterventional, retrospective, observational study was performed in France from December 21, 2015 to September 30, 2016, using data from medical records of patients with SAA treated with omalizumab. Hospital-based pulmonologists and paediatric 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 noninterventional 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 and 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 eosinophil 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 4–6 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 and extracted data for four time-points: T–12 corresponding to the 12 months prior to omalizumab initiation, T₀ corresponding to time of omalizumab treatment initiation, T_{4–6} corresponding to first effectiveness assessment at 4–6 months of treatment (as required in the omalizumab summary of product characteristics) and T₁₂ 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 T₁₂ (if available) were prior to the study start in December 2015.

Outcomes

The primary outcome was response to omalizumab treatment at T_{4–6} compared with T–12 using three criteria.

1) 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 defined as a “responder” or “nonresponder”, respectively.

2) A decrease in the annual exacerbation rate, with a “responder” defined as having a reduction in the annual exacerbation rate of $\geq 40\%$. An asthma exacerbation was defined as a significant worsening of asthma requiring a short burst of oral corticosteroids (OCSs) 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%).

3) A combination of the GETE evaluation and a $\geq 40\%$ reduction in the annual exacerbation rate (“combined response”).

Response was analysed according to blood eosinophil count ($\text{cells}\cdot\mu\text{L}^{-1}$) measured in the year prior to omalizumab initiation (last measurement available prior to initiation).

Statistical analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Descriptive analyses of qualitative variables are expressed as number of patients for each category and percentage. Quantitative variables are presented as mean and standard deviation for normally distributed variables or as median and interquartile range (IQR) when not. The 95% confidence intervals are indicated for each of the three outcome end-points. The number of missing values is reported for each variable, where indicated. All statistical tests were two-sided and the α risk was set at 5%.

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 paediatric pulmonologists) actively recruited a total of 879 patients who met the eligibility criteria. 872 of these patients, of whom 723 (83%) were adults (age ≥ 18 years) and 149 (17%) were minors (age 6–17 years), were included in the study (figure 1). Seven patients, all ≥ 18 years of age, were excluded from analysis due to incomplete medical records at T4–6 (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 being treated with omalizumab after the first effectiveness assessment at T4–6 and 81% (n=706) had a follow-up at T12, *i.e.* 12 months after omalizumab initiation.

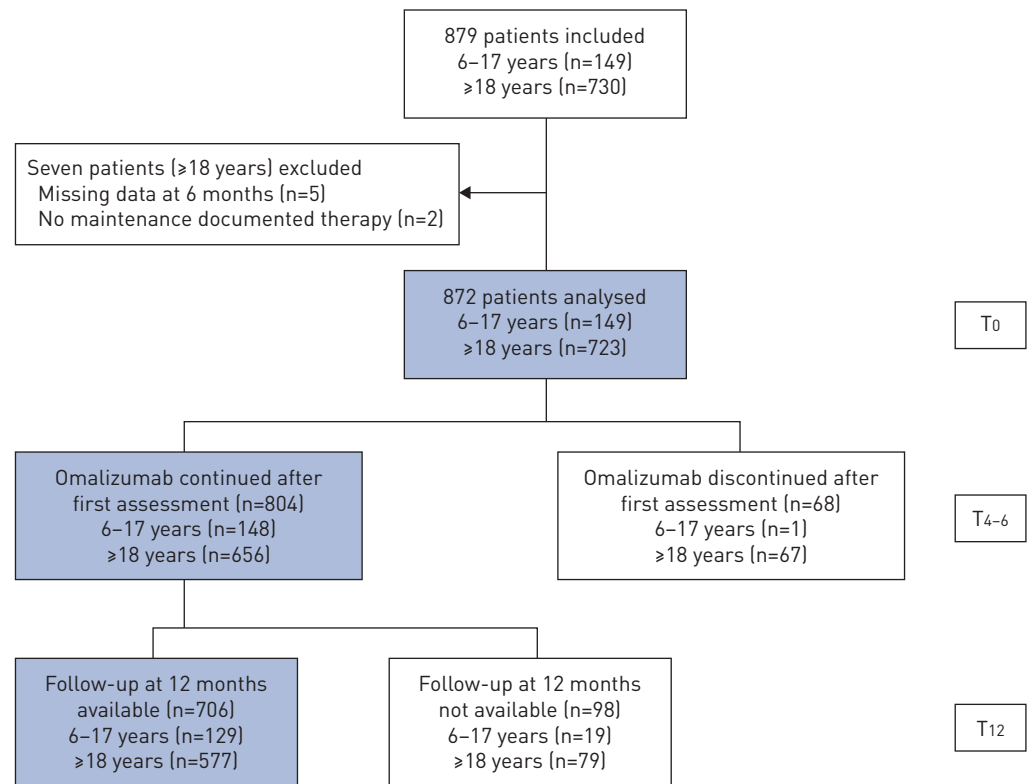


FIGURE 1 Study flowchart. T0: omalizumab treatment initiation; T4–6: first effectiveness assessment after 4–6 months of treatment; T12: effectiveness assessment at 12 months following treatment initiation.

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 corticosteroid (ICS), plus a long-acting β_2 -agonist (LABA) with or without OCS treatment. At T₀, more than a third of the adult patients (n=243 (34.4%)) were treated with OCS maintenance treatment (mean daily dose 20.4 mg·day⁻¹).

All the patients included in this study had uncontrolled SAA, as reflected by the number of asthma events in the previous 12 months (exacerbations: mean±SD 5.2±3.9 in minors and 4.3±3.1 in adults; frequent unplanned hospitalisations: 79 (53%) in minors and 295 (40.8%) in adults). Exacerbations and hospitalisations in the 12 months prior to omalizumab by blood eosinophil count in minors and adults are shown in table 2.

TABLE 1 Demographics and clinical characteristics at T₀ (time of omalizumab initiation) in minors (6–17 years) and adults (≥18 years)

	Minors	Adults	Total
Subjects	149	723	872
Sex			
Male	94 (63.1)	283 (39.1)	377 (43.2)
Female	55 (36.9)	440 (60.9)	495 (56.8)
Age at omalizumab initiation years	11.4±3.1	50.8±14.2	44.1±19.7
Weight kg	45.6±18.1	75.1±16.8	70.0±20.3
Smoking status			
Nonsmoker	142 (97.9)	441 (64.4)	583 (70.2)
Ex-smoker	0 (0)	180 (26.3)	180 (21.7)
Current smoker	3 (2.1)	64 (9.3)	67 (8.1)
Missing	4	38	42
Pack-years (ex-/current smoker)	1	18.0±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)
Angio-oedema	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)
GORD	15 (11)	169 (28.4)	184 (25.2)
Asthma therapy at omalizumab 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⁻¹	17.5±17.7	20.4±14.2	20.3±14.2
Daily dose of ICS $\mu\text{g}\cdot\text{day}^{-1}$ beclomethasone equivalent	1545±615.2	1990.8±1200	1914.7±1134
Hospitalisations in prior 12 months n	2.3±1.9	1.7±1.4	1.9±1.5
Exacerbations in prior 12 months n	5.2±3.9	4.3±3.1	4.5±3.2
Total serum IgE IU·mL⁻¹			
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 eosinophil count in prior 12 months cells·μL^{-1}			
Mean±SD	684.6±507.6	450.6±600.6	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 n, mean±SD or n (%), unless otherwise stated. NSAID: nonsteroidal anti-inflammatory drug; GORD: gastro-oesophageal reflux disease; ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist; OCS: oral corticosteroid; IQR: interquartile range.

TABLE 2 Exacerbations and hospitalisations before omalizumab initiation by blood eosinophil count measured in the year prior to omalizumab initiation (T-12) in minors (6-17 years) and adults (≥18 years)

	<300 cells·µL ⁻¹		≥300 cells·µL ⁻¹		Total	
	Minors	Adults	Minors	Adults	Minors	Adults
Subjects	39	346	110	377	149	723
Exacerbations n	5.1±3.3 (4.1-6.2)	4.2±3.2 (3.9-4.6)	5.2±4.1 (4.4-6.0)	4.4±3 (4.1-4.7)	5.2±3.9 (4.6-5.8)	4.3±3.1 (4.1-4.6)
Hospitalisations n	2.1±1.7 (1.5-2.8)	1.8±1.6 (1.6-2.1)	2.4±2.1 (1.8-2.9)	1.7±1.1 (1.5-1.8)	2.3±1.9 (1.9-2.7)	1.7±1.4 (1.6-1.9)

Data are presented as n or mean±SD (95% CI).

In minors, this severe allergic population was characterised by very high total IgE levels (median IgE level 850 IU·mL⁻¹). In adults, the median total serum IgE level was 285 IU·mL⁻¹.

The median blood eosinophil count at T-12 was more than twice as high in minors compared with adults (619 versus 308 cells·µL⁻¹) (table 3). The distribution of the blood eosinophil count at T-12 ranged from 0 to ≥1000 cells·µL⁻¹ and was on average higher in minors than adults. 377 adult SAA patients (52.1%) had blood eosinophils ≥300 cells·µL⁻¹.

Omalizumab effectiveness was first evaluated at T4-6 by the treating pulmonologist or paediatrician 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 T0 and T4-6, 34.9% of minors (n=52) and 43% of adults (n=311) 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±SD decrease in the annual exacerbation rate was 60.2±88.8% in minors 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 ≥40%): 78.5% (95% CI 71.1-84.8%) of minors and 71.1% (95% CI 67.6-74.4%) of adults.

A combined response to omalizumab treatment (combination of GETE and exacerbation rate decrease) was reached in 67.8% (95% CI 59.7-75.2%) and 58.2% (95% CI 54.5-61.8%) of minors and adults, respectively.

Among the 723 adults, 377 had blood eosinophils ≥300 cells·µL⁻¹ and 346 had blood eosinophils <300 cells·µL⁻¹. In adults, the GETE response, ≥40% reduction of exacerbation response and combined response rates to omalizumab treatment were similar irrespective of the blood eosinophil count, using a cut-off of either 300 or 150 cells·µL⁻¹ (figure 3). Moreover, the proportion of combined response was

TABLE 3 Blood eosinophil counts measured in the 12 months prior to omalizumab initiation (T-12) in minors (6-17 years) and adults (≥18 years)

	Minors	Adults	Total
Subjects	149	723	872
Delay from CBC to omalizumab initiation months	2.8±2.8	3.1±3	3±2.9
OCS maintenance treatment at 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
Eosinophil count cells·µL⁻¹			
<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)

Data are presented as n, mean±SD or n (%). CBC: cell blood count; OCS: oral corticosteroid.

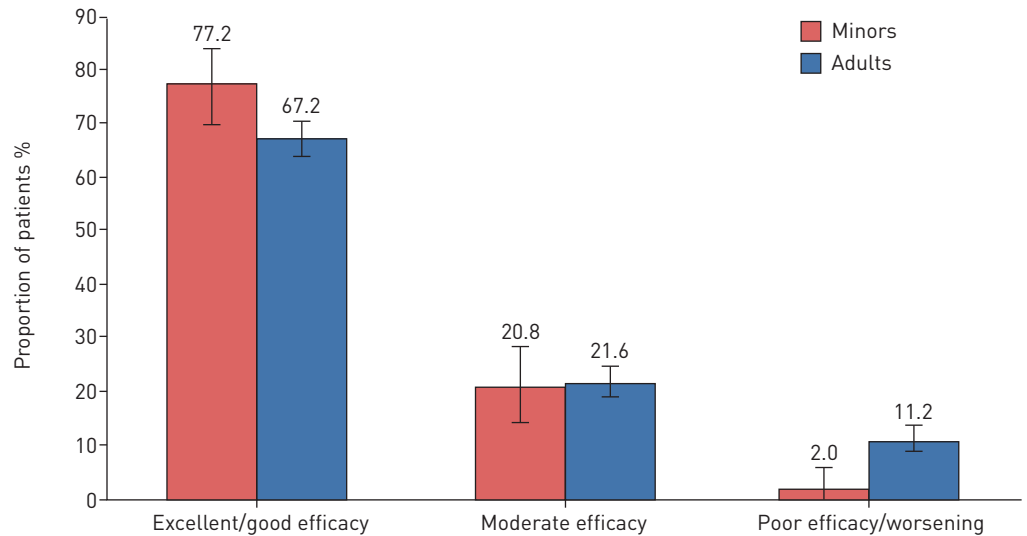


FIGURE 2 Global Evaluation of Treatment Effectiveness evaluation at T₄₋₆ (time of first effectiveness assessment after 4–6 months of treatment) by age group: minors (age 6–17 years; n=149) and adults (age ≥18 years; n=723). Error bars indicate 95% confidence intervals.

similar for “low” eosinophils (<300 cells·μL⁻¹) and “high” eosinophils (≥300 cells·μL⁻¹) in the whole adult population (figure 4).

The percentage reductions in asthma exacerbations in patients with blood eosinophils <300 or ≥300 cells·μL⁻¹ and IgE <75 or ≥75 IU·μL⁻¹ are shown in figure 5, and indicate that omalizumab was effective in all these patient subgroups.

In minors (n=149), 110 had blood eosinophils ≥300 cells·μL⁻¹ and 39 had blood eosinophils <300 cells·μL⁻¹. Responders to omalizumab were also analysed using a cut-off of 600 cells·μL⁻¹. This cut-off was the median blood eosinophil count at T₋₁₂ in this subgroup and allowed a better distribution of the population: 80 patients had blood eosinophils ≥600 cells·μL⁻¹ and 69 patients had blood eosinophils <600 cells·μL⁻¹. Combined response to omalizumab treatment was 70.9% (95% CI 61.5–79.2%) in minors with blood eosinophils ≥300 cells·μL⁻¹ (n=110) and 59% (95% CI 42.1–74.4%) in those with blood eosinophils <300 cells·μL⁻¹ (n=39). With a cut-off of 600 cells·μL⁻¹, combined response reached 72.5% (95% CI 61.4–81.9%) for ≥600 cells·μL⁻¹ (n=80) and 62.3% (95% CI 49.8–73.7%) for <600 cells·μL⁻¹ (n=69).

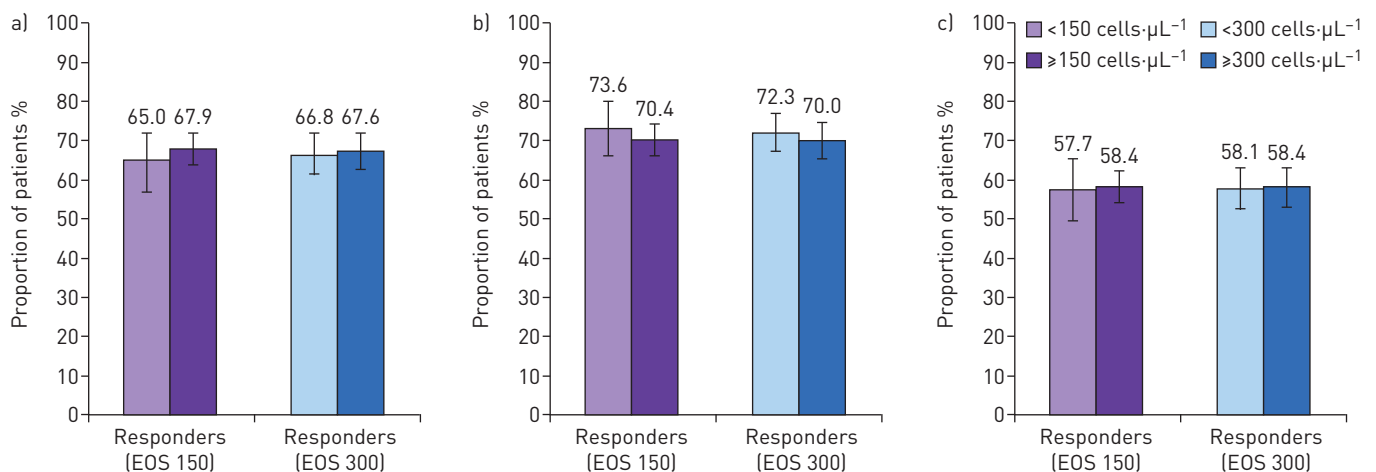


FIGURE 3 Responders to omalizumab treatment in adults (≥18 years) at T₄₋₆ (time of first effectiveness assessment after 4–6 months of treatment) according to blood eosinophil count cut-off at 150 cells·μL⁻¹ (“EOS 150”: <150 cells·μL⁻¹, n=163; ≥150 cells·μL⁻¹, n=560) and 300 cells·μL⁻¹ (“EOS 300”: <300 cells·μL⁻¹, n=346; ≥300 cells·μL⁻¹, n=377). GETE: Global Evaluation of Treatment Effectiveness. a) Responders based on physician’s global evaluation (GETE). b) Responders based on a ≥40% decrease in the annual exacerbation rate. c) Combined responders (combination of GETE and exacerbation rate decrease). Error bars indicate 95% confidence intervals.

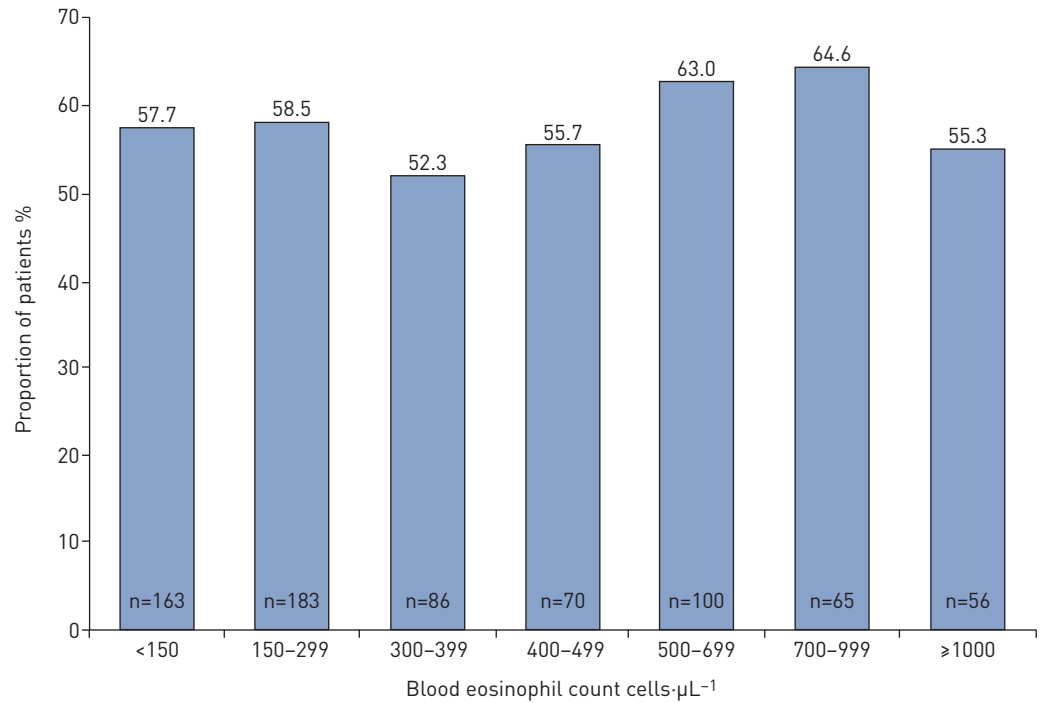


FIGURE 4 Combined responders to omalizumab treatment in adults (≥18 years) according to the distribution of blood eosinophil count in the whole population.

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

At T12, data for treatment effectiveness (including number of exacerbations, hospitalisations 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. 50% of minors (46 out of 92) and 61.9% (179 out of 289) of adults

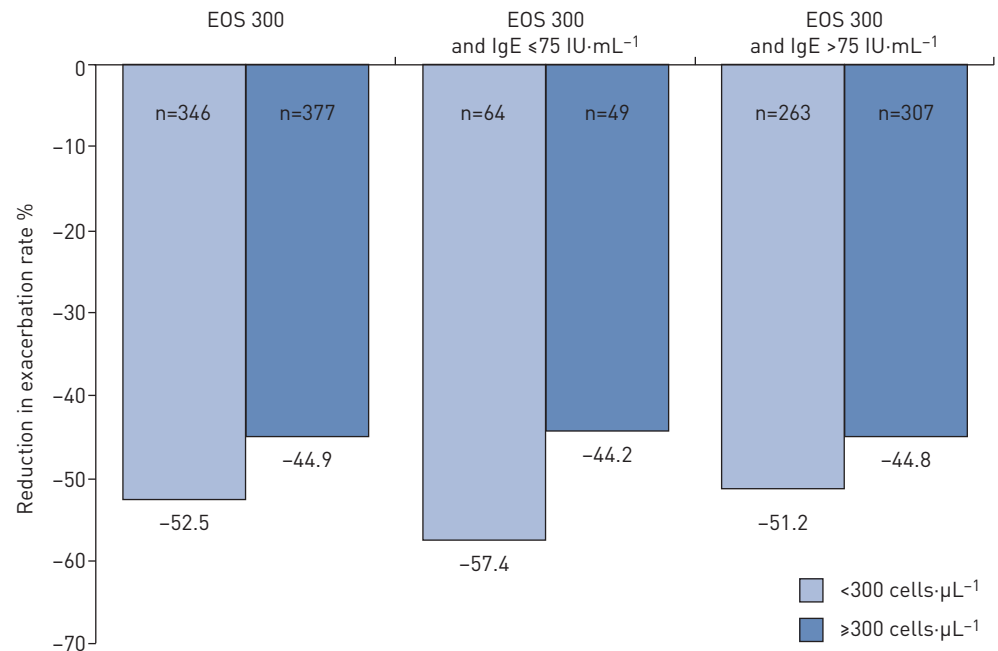


FIGURE 5 Reduction in asthma exacerbation rate according to blood eosinophil count (cut-off 300 cells·µL⁻¹ ("EOS 300")) and serum IgE (cut-off 75 IU·µL⁻¹) in adults (≥18 years) with severe allergic asthma.

TABLE 4 Primary end-points at T₄₋₆ (time of first effectiveness assessment after 4–6 months of treatment) by blood eosinophil count measured in the year prior to omalizumab initiation (T₋₁₂) in minors (6–17 years) and adults (≥18 years)

	<300 cells·μL ⁻¹		≥300 cells·μL ⁻¹		Total	
	Minors	Adults	Minors	Adults	Minors	Adults
Subjects	39	346	110	377	149	723
GETE score[#]						
Responder	25 (64.1) (47.2–78.8)	231 (66.8) (61.5–71.7)	90 (81.8) (73.3–88.5)	255 (67.6) (62.7–72.3)	115 (77.2) (69.6–83.7)	486 (67.2) (63.7–70.6)
Reduction in annual exacerbation rate[¶]						
Exacerbations between T ₀ and T ₄₋₆ n	1.6±1.3	1.7±1.1	2.1±1.6	1.8±1.3	1.9±1.5	1.8±1.2
Annual rate change %	-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	31 (79.5) (63.5–90.7)	250 (72.3) (67.2–76.9)	86 (78.2) (69.3–85.5)	264 (70.0) (65.1–74.6)	117 (78.5) (71.1–84.8)	514 (71.1) (67.6–74.4)
Combination[*]						
Combined responder	23 (59.0) (42.1–74.4)	201 (58.1) (52.7–63.4)	78 (70.9) (61.5–79.2)	220 (58.4) (53.2–63.4)	101 (67.8) (59.7–75.2)	421 (58.2) (54.5–61.8)

Data are presented as n, n (%) [95% CI] or mean±SD. GETE: Global Evaluation of Treatment Effectiveness. [#]: 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 nonresponders (discernible, no appreciable change or worsening)); [¶]: decrease in the yearly rate of exacerbations with omalizumab (a responder has a reduction of ≥40% in the yearly occurrence of exacerbations before and after omalizumab initiation); ^{*}: combination of both definitions (GETE and exacerbation rate decrease).

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±67.8% in adults. 15.5% of minors (20 out of 129) and 10.9% of adults (63 out of 577) were hospitalised at least once during the 12 months of treatment (mean±SD 0.2±0.6 and 0.2±0.6, respectively). The annual rate of hospitalisations was on average the same in minors and adults (mean±SD 0.2±0.6). Compared with the 12 month pre-treatment period, the mean reduction in hospitalisation rates was 73.2% in minors and 72.6% in adults.

A total of 243 adults were treated with OCS (mean daily dose 20.4 mg·day⁻¹) at T₀. 195 patients (80.2%) with OCS as maintenance treatment at T₀ had a follow-up visit available at T₁₂. At T₁₂, 96 of these patients (49.2%) had completely discontinued OCS therapy. Among those who were still being treated with an OCS, the majority (62.1%) had decreased their median (IQR) daily dose by 10 (5–15) mg·day⁻¹, which represented a median (IQR) reduction in daily OCS dose of 50% (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 blood eosinophils <300 and ≥300 cells·μL⁻¹ (data not shown).

Information on blood eosinophil count at 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 blood eosinophil count, while good (n=88) and nonresponders (n=48) had a median decrease only of 20.1% and 0%, respectively. Similar results were observed in minors, with a 55.7% and 53.3% decrease in excellent (n=11) and good (n=17) responders, while nonresponders (n=10) presented a decrease of 11.4%. These results suggest a decrease of the blood eosinophil count when SAA patients respond to omalizumab. The change was not statistically correlated to response status (ANOVA).

68 children (50 males (74%)) were in the 6–12-year-old age group (mean±SD age 8.6±1.7 years at omalizumab initiation). The median blood eosinophil count was 776 cells·μL⁻¹ and was ≥300 cells·μL⁻¹ in 74% of cases. Omalizumab effectiveness evaluated at T₄₋₆ by the treating pulmonologist or paediatrician 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%) for blood eosinophils <300 cells·μL⁻¹ and 83.7% (95% CI 70.3–92.7%) for blood eosinophils ≥300 cells·μL⁻¹. The mean±SD yearly rate of asthma exacerbations decreased from 5.7±3.3 prior to omalizumab therapy to 1.4±3.3 at T₄₋₆. Combined response to omalizumab treatment was reached in 75% (95% CI 63.0–84.7%) of cases, 68.4% (43.5–87.4%) for blood eosinophils <300 cells·μL⁻¹ and 77.6% (63.4–88.2%) for blood eosinophils ≥300 cells·μL⁻¹.

64 patients were current smokers and 180 were ex-smokers (mean±SD 18.0±13.4 pack-years). There was a trend for reduced effectiveness in current and ex-smokers versus nonsmokers. Combined response to omalizumab treatment was reached in 48.4% (95% CI 36.2–60.7%) of current smokers, 55.6% (95% CI 48.3–62.81%) of ex-smokers and 61.2% (95% CI 56.7–65.8%) of nonsmokers. When the blood eosinophil

count was <300 cells· μL^{-1} , combined response was reached in 42.5% (95% CI 27.2–57.8%) of current smokers, 56.8% (95% CI 46.5–67.2%) of ex-smokers and 62.0% (95% CI 55.3–68.7%) of nonsmokers.

Discussion

This report suggests that omalizumab response in patients with SAA does not vary with blood eosinophil count: omalizumab appears to be as effective in patients with “high” eosinophils (≥ 300 cells· μL^{-1}) as in those with “low” eosinophils (<300 cells· μL^{-1}). These results remain similar with all other studied blood eosinophil cut-offs and for all definitions of response.

These real-life findings confirm those already published in the omalizumab arm of the EXTRA study *post hoc* analysis that showed similar exacerbation rates during the 48-week omalizumab treatment period in low (<260 cells· μL^{-1} at baseline) and high (≥ 260 cells· μL^{-1} at baseline) eosinophil subgroups of 0.65 and 0.70, respectively [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 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 eosinophil count [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 *versus* lower eosinophil count [20]. In the latter study, only 3% of patients had been hospitalised for an exacerbation in the previous year, suggesting that patients had moderate to severe asthma, while a 45% reduction in exacerbation rate with omalizumab in patients with a low eosinophil count at baseline showed clinical effectiveness even with low eosinophils [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 randomised, 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 eosinophil count, this does not rule out the effectiveness of omalizumab treatment.

The STELLAIR study provides new data regarding the distribution of eosinophil count in SAA patients before starting Global Initiative for Asthma Step 5 therapies (add-on with either tiotropium, anti-IgE or anti-IL-5 therapies). The study shows different mean blood eosinophil counts for adults (451 cells· μL^{-1}) and minors (685 cells· μL^{-1}) in the 12 months prior to omalizumab initiation. 73.8% of minors and 52.1% of adults had blood eosinophils ≥ 300 cells· μL^{-1} . Such adults could be eligible for anti-IL-5 therapies. This figure could be underestimated as a number of patients were treated by OCSs. In a *post hoc* analysis of the INNOVATE clinical trial [19], 59% (245 patients) of the 12–75-year-old patients had blood eosinophils ≥ 300 cells· μL^{-1} at baseline. Similar results were found in a *post hoc* analysis of the EXTRA trial with 52% of patients having a median baseline blood eosinophil count ≥ 260 cells· μL^{-1} [18]. The proportions of patients with SAA and blood eosinophils ≥ 300 cells· μL^{-1} are close for these three studies that assessed patients with severe asthma eligible for biotherapy. A cut-off of 400 cells· μL^{-1} has also been used in several publications focusing on eosinophil count in asthmatic patients whatever the severity [21, 22]; these studies showed a prevalence rate of 18–26% of patients with blood eosinophils ≥ 400 cells· μL^{-1} . A recent large UK cohort of 130 000 asthmatic patients found blood eosinophils >400 cells· μL^{-1} in 16% of patients (and in 26% of severe patients) (Step 4 and 5 according to the British Thoracic Society therapy steps) [23]. In our study, 40% of adults had blood eosinophils ≥ 400 cells· μL^{-1} 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 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 minors 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 electronic case report form that was developed to minimise missing data using appropriate controls, particularly for end-points 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 that completely converged. Finally, the STELLAIR study is the largest real-world omalizumab study conducted in France, including $>10\%$ of all omalizumab-treated SAA patients in the country. Taken together, it is likely that these results can be generalised to SAA patients eligible for omalizumab and managed by pulmonologists and paediatricians in France and other comparable settings.

Although various biological 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 eosinophil count. 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 eosinophil count.

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