

Higher blood eosinophil levels after omalizumab treatment may be associated with poorer asthma outcomes



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Clinical Implications

- A reduced omalizumab response may be associated with persistent eosinophilic inflammation. Other antieosinophilic treatments should be considered for such patients.

TO THE EDITOR:

Eosinophilic asthma is characterized by high eosinophil levels in induced sputum and peripheral blood. Elevated airway eosinophil counts can be detected in more than 50% of asthmatics and associated with more symptoms, frequent exacerbations, and greater airflow limitation.¹ Increased blood eosinophils (BEs) also predict a greater response to new biological therapies (mepolizumab, reslizumab).² Higher pretreatment BE levels are also related to a better response to omalizumab,³ which reduces BE, fractional exhaled nitric oxide (FENO), serum periostin, and exacerbations.^{4,5} Therefore, a higher effect on eosinophil count reduction may lead to greater clinical improvements. Accordingly, if omalizumab response is eosinophilic dependent, it might be reduced in subjects with persistent high BE counts after anti-IgE therapy.

We explored whether changes in forced expiratory volume in 1 second (FEV₁), Asthma Control Test (ACT), FENO, exacerbation rate, inhaled corticosteroid (ICS) doses, and short-acting bronchodilator use were associated with BE counts measured after a long-term treatment. A total of 170 omalizumab responder subjects (treated for at least 1 year) were retrospectively evaluated. All showed an “excellent”/“good” physician-reported global evaluation of treatment effectiveness (GETE), based on asthma exacerbations and symptoms. Considering BE counts obtained after each patient’s treatment period, subjects were divided into 2 groups. Group 1 showed BE counts of ≤ 300 cells/ μ L (97 subjects), whereas group 2 highlighted BE counts > 300 cells/ μ L (73 subjects). A subgroup with BE counts > 400 cells/ μ L (52 subjects) was also considered (Table 1).

Anthropometric data, comorbidities, allergic sensitizations, ICS dosages, and omalizumab treatment length were similar in the above groups except for pretreatment total serum IgE, which was lower in subjects with eosinophils ≤ 300 cells/mL (Table 1).

Although pretreatment BE counts were known only in 78 (among 170 patients), we observed significantly lower pretreatment FEV₁% and ACT in subjects with BE counts ≤ 300 cells/ μ L, compared with those showing BE > 300 cells/ μ L (Table 1). In contrast, baseline FENO values and the number of subjects with at least 1 exacerbation during the year before treatment were similar in the 2 groups. High ICS doses were taken by the same number of patients with different BE counts before anti-IgE treatment. Patients with BE > 400 cells/ μ L showed the same pretreatment characteristics as in subjects with BE > 300 cells/ μ L.

After anti-IgE therapy, subjects with persistent higher BE counts (> 300 cells/mL) had a lower FEV₁%, increased FENO levels, were more likely to have had at least 1 exacerbation, and were taking higher ICS doses when compared with patients showing eosinophils ≤ 300 cells/mL (Table 1). We also found less improvement after therapy in the various outcomes considered in subjects with persisting BE > 300 cells/mL in comparison with the improvement observed in patients with lower BE counts (Table 1).

Changes in BE counts after omalizumab therapy were considered in the 78 patients whose BE pretreatment values were known. A median of 120 cells/ μ L changes was used as an arbitrary cutoff to divide them into 40/38 subjects with a lower/greater eosinophil reduction, respectively. This cutoff was calculated by subtracting post-treatment from pretreatment values. FEV₁ median changes of 19% (9% to 26%) and 11% (3% to 14%) ($P = .001$) were observed in subjects with variations of BE $>$ or ≤ 120 cells/ μ L, respectively (Figure 1, A). ACT changes were 8 (5-9) and 4 (2-6) ($P = .0001$; Figure 1, B), whereas FENO values were -20 (-24 to -14) and -9 (-21 to 0) ($P = .015$; Figure 1, C). Exacerbation number changes were similar in the 2 groups with different BE variations (-3 [-5 to -2] and -3 [-5 to -2]; $P = .270$; Figure 1, D). However, 25% of subjects with BE ≤ 120 cells/ μ L showed > 3 exacerbation reductions versus 40% in patients with BE > 120 cells/ μ L ($P = .09$; Figure 1, E). Furthermore, 25% of individuals with BE ≤ 120 cells/ μ L and 50% of the population with BE > 120 cells/ μ L used lower ICS doses ($P = .022$; Figure 1, F).

This study observed a reduced response in subjects showing high BE counts after long-term omalizumab treatment. In addition, a higher BE reduction was associated with a greater improvement in FEV₁, ACT, exacerbations, FENO levels, and with higher ICS dose reductions. The BE decrease might be one of the main response indicators in severe eosinophilic asthma.

Omalizumab, neutralizing IgE, prevents the interaction with cellular IgE receptors and downregulates the expression of high-affinity IgE receptors on inflammatory cells, consequently leading to eosinophil reduction both in blood and airways.⁴⁻⁶ Such omalizumab-induced BE reduction has been previously associated with reduced exacerbations, increased FEV₁, and improved GETE.^{4,5} Riccio et al⁶ confirmed that eosinophils decreased by approximately 10-fold in omalizumab responders’ bronchial biopsy, with a consequent reduction in airway remodeling, whereas eosinophils increased by 2-fold to 10-fold in nonresponders. Our study also highlights a relationship between eosinophils and therapy response indicating that a greater reduction may be associated with better asthma outcomes.

TABLE I. Outcomes obtained in subjects with low/high blood eosinophil counts measured before and after long-term omalizumab treatment

	BE ≤300 cells/μL Omalizumab pretreatment	BE >300 cells/μL Omalizumab pretreatment	P	BE ≤300 cells/μL After omalizumab	BE >300 cells/μL After omalizumab	P	BE >400 cells/μL After omalizumab	P
Subjects (%)	28 (35.9%)	50 (64.1%)	.294	97 (57)	73 (43)	.160	52 (30.6)	.015
M/F	10/18	24/26		33/64	27/46		18/34	
Age	56.5 ± 17.4	54.8 ± 11.7	.653	54 ± 14.5	52.6 ± 12.2	.503	53.5 ± 12.4	.946
Months of omalizumab therapy	—	—	—	32.7 ± 20	32.4 ± 19	.934	29.8 ± 16.2	.225
Total serum IgE (UI/mL)	283.5 ± 163.5	441.4 ± 560.2	.150	375 ± 246	456 ± 360	.098	494 ± 396	.022
FEV ₁ %	62.1 ± 13.9*	69.7 ± 13.4	.008	73.16 ± 20.56*	66.92 ± 18.92	.047	67 ± 18	.070
No. of exacerbations in the previous year	5.4 ± 3.2 [#]	4.3 ± 1.6 [°]	.160	0.56 ± 0.88 [#]	0.8 ± 0.92 [°]	.11	0.9 ± 0.94	.062
No. of subjects without exacerbations in the previous year	— [^]	2 (4%) [§]	.284	62 (63.9%) [^]	34 (47.2%) [§]	.03	23 (45.1%)	.043
No. of subjects with exacerbations more than once a year (in the previous year)	28 (100%) [^]	48 (96%) [§]		35 (36.1%) [^]	38 (52.8%) [§]		28 (54.9%)	
FENO (ppb)	39.7 ± 16.6 [†]	54.6 ± 37.7	.140	26.64 ± 18.31 [†]	53.85 ± 61.60	.005	53.35 ± 59.56	.037
Subjects with FENO >25 ppb (%)	12 (70.6%) [♦]	37 (97.4%) [†]	.003	15 (39.5%) [♦]	29 (61.7%) [†]	.041	18 (64.3%)	.038
Subjects with FENO ≤25 ppb (%)	5 (29.4%) [♦]	1 (2.6%) [†]		23 (60.5%) [♦]	18 (38.3%) [†]		10 (35.7%)	
ACT	13.6 ± 3.5 [‡]	15.5 ± 2.6 [●]	.008	20.1 ± 4.5 [‡]	19.8 ± 4.2 [●]	.691	19.8 ± 4.4	.656
Subjects with ACT ≥20 (%)	— [▲]	1 (2%) ^Δ	.451	61 (62.9%) [▲]	47 (64.4%) ^Δ	.841	33 (63.5%)	.990
Subjects with ACT <20 (%)	28 (100%) [▲]	49 (98%) ^Δ		36 (37.1%) [▲]	26 (35.6%) ^Δ		19 (36.5%)	
No control	19 (67.9%) ^Σ	39 (78%) ^X	.325	26 (26.8%) ^Σ	23 (31.5%) ^X	.637	19 (36.5%)	.204
Partial control	9 (32.1%) ^Σ	11 (22%) ^X		47 (48.5%) ^Σ	36 (49.3%) ^X		25 (48.1%)	
Good control	— ^Σ	— ^X		24 (24.7%) ^Σ	14 (19.2%) ^X		8 (15.4%)	
No SABA use in the previous month	5 (17.8%) ^Φ	5 (10%) ^λ	.319	53 (60.9%) ^Φ	36 (54.5%) ^λ	.429	27 (58.7%)	.518
SABA use more than once in the previous month	23 (82.2%) ^Φ	45 (90%) ^λ		34 (39.1%) ^Φ	30 (45.5%) ^λ		19 (41.3%)	
Unchanged level of therapy	—	—		48 (57.8%)	36 (58.1%)	.762	27 (60%)	.925
Step-up of therapy	—	—		3 (3.6%)	1 (1.6%)		1 (2.2%)	
Step down of therapy	—	—		32 (38.6%)	25 (40.3%)		17 (37.8%)	
Low dose of ICS therapy	— ^Υ	3 (6%)	.161	6 (9.4%) ^Υ	9 (10.5%)	.012	10 (9.4%)	.059
Medium dose of ICS therapy	10 (35.7%) ^Υ	10 (20%)		32 (50%) ^Υ	23 (26.7%)		33 (31.1%)	
High dose of ICS therapy	18 (64.3%) ^Υ	37 (74%)		26 (40.6%) ^Υ	54 (62.8%)		63 (59.4%)	

Variables are expressed as means ± standard deviations or as numbers of cases (percentages). Comparisons were made by using the analysis of variance test or by using the χ^2 test; subjects with blood eosinophils ≤300 cells/μL were considered as the reference group (in post-treatment comparisons). Bold indicates statistical significance ($P < .05$). No, partial, or good control was evaluated according to GINA guidelines considering the frequency of diurnal/nocturnal symptoms, rescue medication use, limitations in daily life in the last month, and exacerbations in the last year and FEV₁ value. Pretreatment data were calculated considering 78 patients whose eosinophil count was known before omalizumab treatment. Comparisons between pretreatment and post-treatment results in subjects with BE ≤300 cells/μL (* $P = .008$; [#] $P = .0001$; [†] $P = .0009$; [♦] $P = .032$; [‡] $P = .0001$; [§] $P = .0007$; ^Φ $P = .0001$; ^Υ $P = .06$) and with BE >300 cells/μL ([°] $P = .0001$; ^Δ $P = .0001$).

ACT, Asthma Control Test; BE, bronchial eosinophils; FENO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; SABA, short-acting bronchodilators.

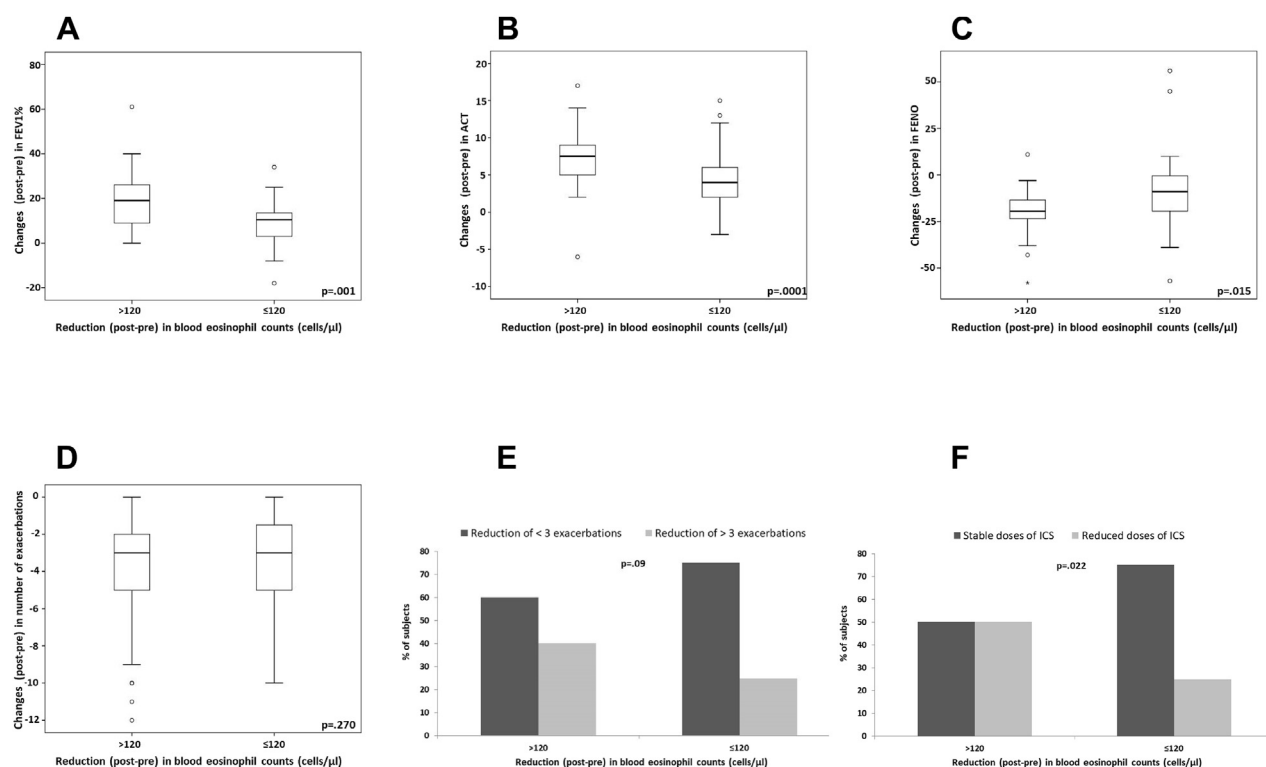


FIGURE 1. Changes in FEV₁ % (A), ACT (B), FENO (C), number of exacerbations (D, E), and ICS doses (F) obtained in 38 asthmatics with a high (>120 cells/μL) and in 40 subjects with a low (≤120 cells/μL) reduction in blood eosinophils after a long-term omalizumab treatment (median of 30 months). All variations were calculated by subtracting the post-value (after omalizumab) from the pretreatment value (before omalizumab therapy). Comparisons were made by using the Mann-Whitney and χ^2 tests. ACT, Asthma Control Test; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid.

A total of 43% of patients showed post-treatment BE >300 cells/μL, whereas 50% had the BE decrease <120 cells/μL after treatment; both results were associated with a reduced response. Probably, serum-free IgE reduction by omalizumab is associated with a significant BE count reduction in moderate-to-severe allergic asthmatics and^{5,7} serum-free IgE decrease to normal concentrations after omalizumab seems necessary for consistent therapeutic responses.⁷ However, 19% to 26% of subjects, even after several weeks of treatment, may show a nonsignificant free IgE reduction⁷ that may lessen the effect on eosinophils and reduce omalizumab effectiveness. It is not known whether increasing the omalizumab dose in such patients would be associated with greater effectiveness.

Some factors (age, obesity, smoking, nasal polyposis, and allergic polysensitization) may reduce anti-IgE response,⁸ and some comorbidities (especially pneumonia and sinusitis/nasal polyps) are associated with BE >300 cells/μL.⁹ Such factors combined with a hypereosinophilic status may further reduce omalizumab effectiveness.

In conclusion, in this real-world study, some severe allergic asthmatics may show higher BE counts and/or low BE reductions after anti-IgE treatment. This persistent hypereosinophilic status may be associated with a reduced omalizumab

effectiveness. Other antieosinophilic treatments should be considered for such patients.

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