

Anti-IgE Monoclonal Antibody (Omalizumab) in Refractory and Relapsing Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss)

Data on Seventeen Patients

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Objective. To describe the efficacy and safety of omalizumab, an anti-IgE monoclonal antibody, in patients with refractory and/or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA).

Methods. We conducted a nationwide retrospective study including EGPA patients who received omalizumab. Response was defined as the absence of asthma and/or sinonasal exacerbations with a prednisone dos-

age of ≤ 7.5 mg/day (complete response) or >7.5 mg/day (partial response).

Results. Seventeen patients (median age 45 years) received omalizumab for severe steroid-dependent asthma (88%) and/or sinonasal involvement (18%). After a median follow-up of 22 months, 6 patients (35%) achieved a complete response, 5 patients (30%) achieved a partial response, and 6 patients (35%) had no improvement. The median Birmingham Vasculitis Activity Score decreased from 2.5 at baseline to 0.5 at 12 months. The median number of exacerbations per month decreased from 1 at baseline to 0 at 12 months, and the median forced expiratory volume in 1 second increased from 63% of the percent predicted at baseline to 85% of the percent predicted at 12 months. The median prednisone dosage decreased from 16 mg/day at baseline to 11 mg/day at 6 months and 9 mg/day at 12 months. Omalizumab was discontinued in 8 patients

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(47%) during follow-up, because of remission (12.5%), adverse event despite disease remission (12.5%), refractory disease (25%), or relapse (50%). Relapses included retrobulbar optic neuritis attributable to EGPA in 2 patients and severe asthma flare in 2 others.

Conclusion. The results of this study suggest that omalizumab may have a corticosteroid-sparing effect in EGPA patients with asthmatic and/or sinonasal manifestations, but reducing the corticosteroid dose may also increase the risk of severe EGPA flares, which raises the question of the safety of omalizumab in patients with EGPA.

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) is a rare systemic small-vessel vasculitis associated with asthma and blood and tissue eosinophilia (1). EGPA belongs to the group of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides and commonly involves both the upper and lower respiratory tracts, the lungs, the peripheral nerve, and the heart (2,3). ANCAs are positive in 31–38% of patients with EGPA and display a perinuclear labeling pattern on immunofluorescence analysis that is directed mainly against myeloperoxidase (MPO) (2,4). ANCA-positive patients are likely to develop vasculitis manifestations of the disease (e.g., glomerulonephritis and peripheral neuropathy), whereas ANCA-negative patients more frequently have cardiac manifestations, including cardiomyopathy and/or myocarditis (4–6).

Therapeutic management is based on corticosteroids alone or in combination with conventional immunosuppressive agents (mainly azathioprine, methotrexate, or cyclophosphamide), according to disease severity as assessed by the Five-Factors Score (7). Such treatments, in addition to their common side effects, are frequently insufficiently effective to control chronic asthma and/or rhinosinusitis, the treatment of which requires long-term high-dose corticosteroids (8–12). Because EGPA shares common pathophysiologic features with eosinophilic disorders and asthma, new therapeutic options that are used in these conditions are being evaluated for treatment of EGPA. Mepolizumab, a monoclonal antibody targeting interleukin-5 (IL-5), the major eosinophil survival factor, has shown promising results in 2 small preliminary studies (13,14) and is currently being evaluated in a randomized trial.

Besides the pivotal role of IL-5 in the pathogenesis of EGPA, other Th2-related cytokines (i.e., IL-4 and IL-13) are involved by precipitating B cell responses resulting in increased production of IgG4, IgE, and ANCA (6,15,16). Strongly elevated IgE and IgG4 levels are common in EGPA patients (16). In patients with

asthma, IgE could be responsible for the degranulation of IgE receptor-bearing cells (e.g., eosinophils, basophils, and mast cells). Omalizumab is a recombinant humanized monoclonal antibody targeting the high-affinity receptor binding site on IgE. The binding of omalizumab to free IgE prevents its interaction with both high-affinity and low-affinity receptors (Fcε receptor I [FcεRI] and FcεRII, respectively) found on the surface of mast cells, basophils, eosinophils, and B cells. Omalizumab also induces eosinophil apoptosis and down-regulates the production of inflammatory cytokines, thus exhibiting antiallergic and antiinflammatory properties (17). Finally, omalizumab has proven efficacy for the treatment of allergic asthma (18) and allergic rhinitis (19), with a favorable safety profile (20).

In the literature, data for EGPA are rare and conflicting. Some case reports suggest that omalizumab might be effective in patients with active disease (21–27), but others suggest a temporal association between omalizumab treatment and the development of EGPA (28–35), thus raising the question of a causal relationship between anti-IgE therapy and disease onset. These findings have dramatically hindered the use of omalizumab for treatment of EGPA. Therefore, we sought to describe our findings with respect to the effects of omalizumab treatment on asthma, ear, nose, and throat (ENT), and vasculitis manifestations in patients with refractory and/or relapsing EGPA and to evaluate the indications, efficacy, and safety of omalizumab.

PATIENTS AND METHODS

Patients. We performed a nationwide retrospective multicenter study of patients from 10 French internal medicine and pulmonology departments. The inclusion criteria were: 1) a diagnosis of EGPA according to the American College of Rheumatology 1990 criteria (36) and/or the European Medicines Agency (EMA) algorithm (37) and/or the definition of EGPA adopted by the 2012 Chapel Hill Consensus Conference (1), and 2) treatment with at least 1 injection of omalizumab. Patients were included between 2007 and 2014. Given the retrospective design of the study and the small number of patients, all patients with EGPA who received omalizumab were included, regardless of the indication, the number of previous exacerbations, and previous treatment lines. Patients could be included because of uncontrolled disease related to active vasculitis, uncontrolled asthma, and/or ENT manifestations. The definitions of refractory or relapsing vasculitis were in accordance with the European League Against Rheumatism (EULAR) recommendations (11). Uncontrolled asthma and ENT manifestations were defined as recurrent and steroid-dependent asthma exacerbations (no predefined lower limit) and as steroid-dependent disabling ENT manifestations, respectively, at the discretion of the clinician in charge of the patient. This study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of

Helsinki principles and was approved by the local Institutional Review Board.

Baseline measurements. Using a standardized case report form, clinical and biologic data were retrospectively collected by the physician providing care at the time of EGPA diagnosis, the time of initiation of omalizumab, and during follow-up. Assessments included clinical manifestations, eosinophil count, serum C-reactive protein (CRP) level, serum creatinine level, IgE level, ANCA titer and specificity, urinalysis to screen for hematuria and urine protein excretion, and treatment characteristics before and 3, 6, 12, 18, and 24 months after the initiation of omalizumab. The Birmingham Vasculitis Activity Score (BVAS) (38) was used to assess disease activity, and the Vasculitis Damage Index (39) was used to assess damage at baseline and during follow-up. Both scores were assessed retrospectively.

Treatment protocol, outcome, and response to therapy. Omalizumab was administered subcutaneously once or twice per month. Given the retrospective design of this study, the dosage for each patient was defined by the practitioner in charge. The dosage was calculated according to the patient's IgE levels and body weight as suggested for severe asthma treatment, in accordance with the EMA recommendations.

The characteristics of the patients at the time of the initiation of omalizumab are referred to as baseline characteristics. Clinical response was defined by analyzing the course of asthma (exacerbations, peak flow measurement, spirometry), rhinosinusitis manifestations, vasculitis manifestations assessed using the BVAS, prednisone dosage, eosinophil count, IgE, and CRP levels. Based on the EGPA Task Force recommendations, ENT manifestations such as rhinitis or sinusitis, asthma flares, and/or eosinophilia $<1,000/\text{mm}^3$ may not reflect vasculitis activity in the absence of other vasculitis manifestations (40). In addition, EULAR experts recommended that the definition of complete response should include a prednisone dosage of ≤ 7.5 mg/day to control systemic manifestations (9).

In order to assess the efficacy of omalizumab, complete response was defined as the absence of asthma and/or ENT exacerbations with a prednisone dosage of ≤ 7.5 mg/day, and partial response was defined as the absence of asthma and/or ENT exacerbations with a prednisone dosage of >7.5 mg/day. Refractory disease was defined as the absence of improvement with omalizumab, i.e., persistent asthma and/or ENT exacerbations with a prednisone dosage of >7.5 mg/day. Relapsing disease was defined as initial improvement with complete response or partial response followed by disease flare. These definitions were formulated according to the recommendations of the EGPA Task Force and EULAR experts and approved for use in routine clinical practice (9,40). Patients with refractory and/or relapsing EGPA had active asthma and/or ENT involvement and possibly, in some cases, active vasculitis manifestations such as cutaneous or musculoskeletal involvement. Patients with recurrent asthma exacerbations were arbitrarily limited to a maximum of 1 exacerbation per week (4 exacerbations per month). We also recorded adverse effects during follow-up.

Statistical analysis. Descriptive characteristics are reported as the mean $\pm$ SD for continuous variables and the median (range) for categorical variables. Qualitative variables were compared using Fisher's exact test, and continuous variables were compared using the nonparametric Mann-Whitney test. We also compared some of the measures obtained at

Table 1. Characteristics of the omalizumab-treated patients (n = 17) at the time of EGPA diagnosis*

Female	7 (41)
Age at EGPA diagnosis, median (range) years	45 (17–82)
Age at initiation of omalizumab, median (range) years	52 (18–87)
Clinical manifestations at EGPA diagnosis	
Asthma	17 (100)
Duration, median (range) years	2 (0–41)
ENT involvement	16 (94)
Non-fixed pulmonary infiltrates	9 (53)
Constitutional symptoms	9 (53)
Cutaneous involvement	8 (47)
Arthralgia or arthritis	6 (35)
Peripheral nervous system involvement	5 (29)
Cardiac involvement	4 (24)
Ocular involvement	2 (12)
Central nervous system involvement	1 (6)
Renal involvement	0
Laboratory findings	
Blood eosinophilia	17 (100)
Eosinophil count, median (range) mm^3	4,965 (850–23,530)
Serum IgE, median (range) IU/ml	1,970 (28–7,503)
ANCA positivity	5 (29)
C-reactive protein, median (range) mg/liter	57 (3–218)
Previous treatments	
No. of previous treatments before omalizumab, median (range)	3 (1–5)
Time from first EGPA treatment to initiation of omalizumab, median (range) months	78 (8–171)
Oral corticosteroids	17 (100)
Methylprednisolone infusions	8 (47)
Azathioprine	14 (82)
Intravenous cyclophosphamide	8 (47)
Methotrexate	5 (29)
Mycophenolate mofetil	2 (12)
Cotrimoxazole	2 (12)
Other	1 (6)

* Except where indicated otherwise, values are the number (%) of patients. EGPA = eosinophilic granulomatosis with polyangiitis (Churg-Strauss); ENT = ear, nose, throat; ANCA = antineutrophil cytoplasmic antibody.

baseline (initiation of omalizumab) with those obtained at months 3, 6, and 12 after the initiation of omalizumab, using Wilcoxon's signed rank test. All tests were 2-sided with a significance level of 0.05. Graphing and statistical analyses were performed using GraphPad Prism version 4.0 and Instat version 3.0 for Windows.

RESULTS

Patient characteristics before omalizumab treatment. Seventeen patients (10 men and 7 women) with a median age of 45 years (range 17–82 years) received at least 1 course of omalizumab for refractory and/or relapsing EGPA. Table 1 shows the characteristics of the patients included in the study. At the time of the diagnosis of EGPA, all patients presented with asthma and blood eosinophilia, and 16 patients (94%) pre-

Table 2. Characteristics associated with disease flares requiring initiation of omalizumab*

Indications for initiation of omalizumab	
Severe steroid-dependent asthma	15 (88)
Severe ENT involvement	3 (18)
High-dose steroid dependency	16 (94)
Pruritus	1 (6)
Active clinical manifestations	
Asthma	17 (100)
No. of exacerbations, median (range)	1 (0–15)
ENT involvement	8 (47)
Non-fixed pulmonary infiltrates	2 (12)
Constitutional symptoms	2 (12)
Arthralgia or arthritis	2 (12)
Cutaneous involvement	2 (12)
Peripheral nervous system involvement	0
Cardiac involvement	0
Renal involvement	0
Laboratory findings	
Eosinophil count, median (range) mm ³	743 (0–2,230)
Serum IgE, median (range) IU/ml	597 (22–3,527)
ANCA positivity	1 (6)
C-reactive protein, median (range) mg/ml	9 (1–64)
Treatments	
Omalizumab combined with corticosteroids	9 (53)
Prednisone dosage, median (range) mg/day	18.5 (9–40)
Omalizumab combined with other immunosuppressive agent	8 (47)
Oral corticosteroids	17 (100)
Prednisone dosage, median (range) mg/day	16 (6–40)
Methylprednisolone infusions	1 (6)
Azathioprine	5 (29)
Methotrexate	2 (12)
Mycophenolate mofetil	1 (6)
Cotrimoxazole	1 (6)
Characteristics of omalizumab treatment	
Duration, median (range) weeks	64 (1–216)
No. of injections, median (range)	18 (1–61)
Dose, median (range) mg	300 (150–600)
Injection interval	
Every 2 weeks	5 (29)
Every 4 weeks	11 (65)
Only 1 injection	1 (6)

* Except where indicated otherwise, values are the number (%) of patients. ENT = ear, nose, throat; ANCA = antineutrophil cytoplasmic antibody.

sented with sinonasal abnormalities, 9 (53%) with pulmonary infiltrates, 5 (29%) with peripheral neuropathy, and 4 (24%) with cardiac involvement. Tissue eosinophilia infiltration in skin or nasal biopsy specimens was documented in 6 patients (35%). The median baseline BVAS was 13 (range 2–31). Five patients (29%) were positive for ANCAs, with MPO specificity in 4 (80%) of these patients. The median number of previous treatment lines before omalizumab initiation was 3 (range 1–5). Previous treatments included corticosteroids in 17 patients (100%) and immunosuppressive or immunomodulatory agents in 15 patients (88%); 14 patients (82%) received azathioprine, 8 patients (47%) received

cyclophosphamide, 5 patients (29%) received methotrexate, 2 patients (12%) received mycophenolate mofetil, and 2 (12%) patients were treated with cotrimoxazole.

Disease flares requiring initiation of omalizumab. Table 2 shows the characteristics of the disease flares that required omalizumab initiation. Omalizumab was used as second-line therapy in 2 patients (12%), third-line therapy in 5 patients (29%), fourth-line therapy in 7 patients (41%), fifth-line therapy in 2 patients (12%), and sixth-line therapy in 1 patient (6%). Fifteen patients (88%) had severe steroid-dependent asthma, and 3 patients (18%) had severe ENT involvement. The median BVAS at the time of omalizumab initiation was 2.5 (range 0–8), reflecting minor vasculitis activity. Omalizumab was administered every 2 weeks in 5 patients (29%) and every 4 weeks in 11 patients (65%); the most common regimen was a 300-mg injection every 4 weeks (41% of patients). The median duration of omalizumab treatment was 64 weeks (range 1–216 weeks), and the median number of injections was 18 (range 1–61).

Therapeutic regimens associated with omalizumab. The therapeutic regimens associated with omalizumab are shown in Table 2. All patients received oral corticosteroids, with an initial median dosage of 16 mg/day (range 6–40), administered in combination with omalizumab in 9 patients (53%). Omalizumab was administered in combination with other immunosuppressants in 8 patients (47%).

Outcome. After a median follow-up of 22 months (range 4–70 months) after omalizumab initiation, 6 patients (35%) achieved a complete response, and 5 patients (30%) achieved a partial response, mainly 3–6 months after treatment initiation. In contrast, 6 patients (35%) had refractory disease. Complete remission was achieved at 3 months in 2 patients, at 6 months in 2 patients, and at 12 months in 1 patient (no data are available for time to response in 1 patient). Partial remission was achieved at 3 months in 3 patients and at 6 months in 1 patient (no data are available for time to response in 1 patient). Improvement in responder patients was most commonly achieved after the third month of treatment.

As shown in Table 3 and Figure 1, the median BVAS dropped from 2.5 at baseline to 1, 1, and 0.5 at months 3, 6, and 12, respectively. The median prednisone dosage decreased from 16 mg/day at baseline to 10 mg/day, 11 mg/day, and 9 mg/day at months 3, 6, and 12, respectively. In contrast, the eosinophil count did not decrease over time (Figure 1C). Regarding asthmatic manifestations, the median forced expiratory volume

Table 3. Outcome variables at different times during follow-up*

Variable	Month 0	Month 3	Month 6	Month 12	After omalizumab discontinuation†
Prednisone dosage, mg/day	16 (6–40)	10 (5–30)	11 (0–40)	9 (0–30)	12.5 (0–60)
BVAS	2.5 (0–8)	1 (0–8)	1 (0–8)	0.5 (0–8)	2 (0–4)
Eosinophil count, mm ³	438 (0–2,230)	516 (120–3,700)	250 (70–1,110)	1,023 (0–6,000)	857 (300–6,000)
CRP, mg/liter	3.75 (2–13.6)	2.75 (2–8)	4.15 (2–11)	5 (2–29)	3 (2–9)
No. of exacerbations/month	1 (0–4)	0 (0–1)	0 (0–0.6)	0 (0–1)	0
FEV ₁ , % predicted	63 (57–123)	91 (54–114)	82 (59–104)	85 (53–105)	68 (53–84)
FEV ₁ /FVC, % predicted	72 (39–98)	77 (70–99)	74 (32–90)	67 (48–91)	58 (41–76)

* Values are the median (range). BVAS = Birmingham Vasculitis Activity Score; CRP = C-reactive protein; FEV₁/FVC = forced expiratory volume in 1 second/forced vital capacity.

† Omalizumab was discontinued in 8 patients due to remission, refractory disease, or relapse. The median follow-up after discontinuation was 25.5 months (range 0–60 months).

in 1 second (FEV₁) increased from 63% at baseline to 91%, 82%, and 85% of predicted at months 3, 6, and 12, respectively, and the median number of exacerbations per month decreased from 1 at baseline to 0 at months 3, 6, and 12. The only significant difference was the prednisone dosage at each time point compared with the baseline value, whereas no significant difference was

noted for the eosinophil count, the BVAS, and the FEV₁ (Figures 1A–D).

Seven patients had other manifestations in addition to asthma and/or ENT involvement. Two patients who had a complete response (absence of asthma and/or sinonasal exacerbations with a prednisone dosage of ≤ 7.5 mg/day) also had cutaneous involvement (1 patient

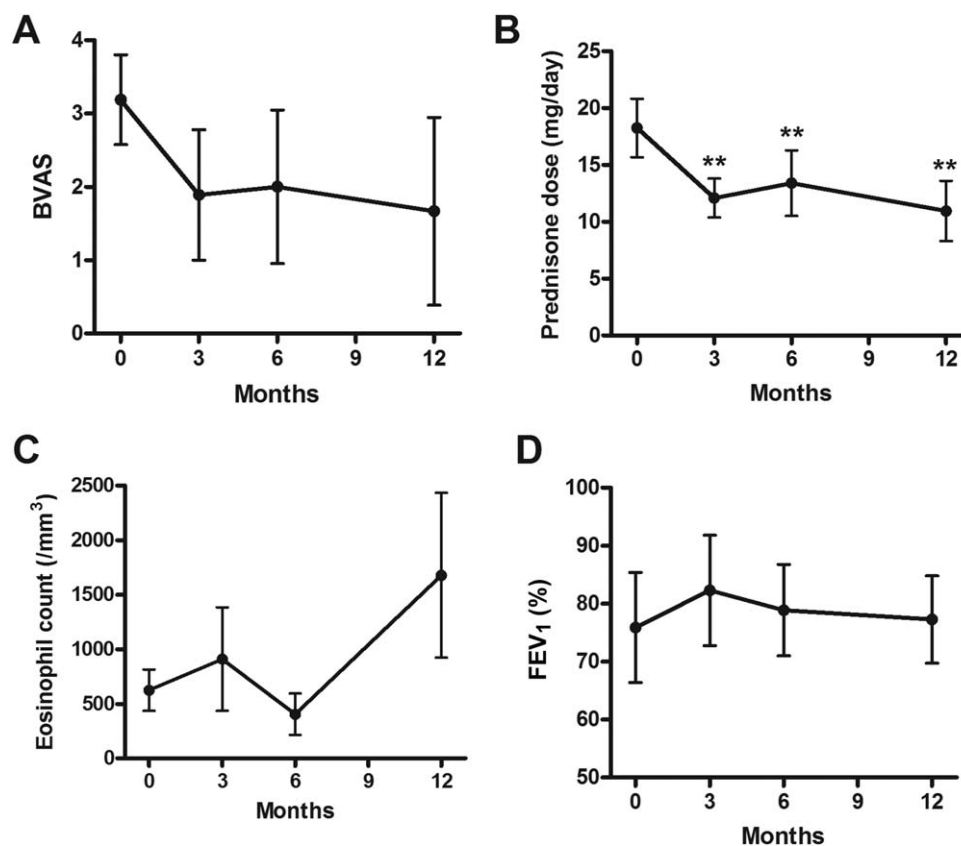


Figure 1. Birmingham Vasculitis Activity Score (BVAS) (A), prednisone dosage (B), eosinophil count (C), and forced expiratory volume in 1 second (FEV₁) (D) during the first 12 months of follow-up after omalizumab initiation. Values are the mean $\pm$ SEM. ** = $P < 0.01$ versus pretreatment.

with urticarial lesions and 1 patient with intense pruritus), and these patients had no response to omalizumab for the cutaneous manifestations. Two patients who had a partial response (absence of asthma and/or sinonasal exacerbations with a prednisone dosage of >7.5 mg/day) also had musculoskeletal involvement (1 patient with arthralgia and 1 patient with myalgia and fever), and these patients had a complete response to omalizumab for the musculoskeletal symptoms. Finally, 3 patients who had no response to omalizumab also had pulmonary infiltrates or asthenia, and they had no response for these manifestations.

Omalizumab was discontinued in 8 patients (47%) during follow-up, because of disease remission in 1 patient (12.5%) and an adverse event despite disease remission in another patient (12.5%) (in both patients, remission was sustained following discontinuation of omalizumab after 5 and 7 months of follow-up, respectively), refractory disease in 2 patients (25%), and disease relapse in the 4 remaining patients (50%). Two of the 4 patients in whom disease relapsed during omalizumab therapy developed retrobulbar optic neuritis after 12 and 15 months of omalizumab treatment, respectively, leading to treatment discontinuation, whereas the 2 others developed severe asthma flares after 1 month and 18 months of omalizumab treatment, respectively. The median follow-up after omalizumab discontinuation was 25.5 months (range 0–60 months). The outcome variables at the last follow-up after omalizumab discontinuation are shown in Table 3.

Case reports of omalizumab-treated patients in whom retrobulbar optic neuritis developed. The first patient, a 46-year-old woman, received omalizumab for severe and corticosteroid-dependent asthma, allowing tapering of prednisone from 30 mg/day to 5 mg/day. Fifteen months after omalizumab initiation, she experienced rapidly progressive bilateral visual impairment (best-corrected visual acuity 1/20) associated with constitutional symptoms, cutaneous lesions with evidence of extravascular granulomas, and biopsy specimens showing eosinophilic infiltrates. The patient's eosinophil count was $1,300/\text{mm}^3$, and the serum CRP level was 218 mg/liter. The results of eye examination and visual evoked potential tests were consistent with a diagnosis of retrobulbar optic neuritis. Magnetic resonance imaging (MRI) of the brain showed bilateral optic neuritis, whereas results of the cerebrospinal fluid (CSF) examination were normal. A diagnosis of optic neuritis related to relapse of EGPA was made, and omalizumab was discontinued. No improvement was observed after treatment with methylprednisolone pulses followed by oral

prednisone associated with azathioprine after 2 years of follow-up.

The second patient, a 53-year-old man, also received omalizumab for severe and corticosteroid-dependent asthma. Twelve months after initiation of omalizumab combined with prednisone and azathioprine, he developed progressive visual impairment in his left eye in association with fever, headaches, and anosmia. Results of the examination were consistent with left retrobulbar optic neuritis, with best-corrected visual acuity 1/10. MRI of the brain showed frontal pachymeningitis, whereas the eosinophil count was normal at $200/\text{mm}^3$, the serum CRP level was 56 mg/liter, and the results of CSF examination were normal. A diagnosis of optic neuritis and pachymeningitis related to relapse of EGPA was made despite a normal eosinophil count, and omalizumab and azathioprine were discontinued. Pulses of methylprednisolone followed by oral prednisone were prescribed in combination with intravenous cyclophosphamide, but there was no visual improvement.

Omalizumab safety. Except for the 2 relapses that occurred during treatment, omalizumab was well tolerated, and no serious adverse event was observed. Adverse events included erythema and pruritus at the injection site ($n = 1$), myalgia ($n = 1$), and asthenia 1 day after injection ($n = 1$). These symptoms resolved without intervention. Omalizumab was discontinued in 1 patient because of leg edema and numbness 6 months after initiation, but there was no evidence of drug causality.

DISCUSSION

EGPA management continue to be a therapeutic challenge. Corticosteroids and conventional immunosuppressive agents are often insufficiently effective to control chronic asthma and/or rhinosinusitis, leading to the long-term use and high doses of corticosteroids, which are associated with significant morbidity (8,10–12). Despite increasing data regarding the use of the immunomodulatory agent armamentarium (e.g., mepolizumab and rituximab) for the treatment of EGPA, an unmet need for glucocorticoid-sparing drugs in EGPA remains. In the current study, we analyzed data for 17 patients with EGPA who received omalizumab, an anti-IgE monoclonal antibody, as adjunctive therapy for refractory and/or relapsing asthmatic and/or sinonasal manifestations. Despite the small sample size in this study, relevant information is pointed out.

First, omalizumab seemed to provide prompt and sustained improvement during the first year of treatment. Indeed, the median prednisone dosage was

tapered from 16 mg/day to 10 mg/day after 3 months of therapy, and this trend continued during the 12 months of follow-up. Given the significant number of adverse events attributable to long-term corticosteroid treatment (41), this decrease in the prednisone dosage is a substantial clinical benefit. Similarly, the number of asthma exacerbations also decreased, and the FEV₁ increased.

In contrast, complete remission according to the EULAR recommendations was achieved only in one-third of the patients (9). Next, given the low BVAS at the onset of omalizumab treatment, and despite a slight decrease in the BVAS during therapy, it was not possible to evaluate the efficacy of omalizumab for vasculitis manifestations. It is, however, important to keep in mind that in this study omalizumab was never indicated for vasculitis-related manifestations.

Most of these results are consistent with those from previous studies showing significant and prompt efficacy of omalizumab for treating the symptoms of asthma and corticosteroid sparing (21,23–27). However, few case reports have described severe disease exacerbations following omalizumab initiation (28–35). In these cases, it is more likely that tapering of systemic corticosteroids unmasked preexisting EGPA rather than omalizumab being directly responsible for EGPA development. Thus, patients might benefit from slow corticosteroid tapering after the onset of omalizumab treatment, given the possibility of EGPA relapse.

In contrast to the effect of omalizumab for asthma manifestations and prednisone tapering, no decrease in the eosinophil count and serum IgE and CRP levels was observed during treatment with omalizumab, which is consistent with the results of the recent study by Grayson et al (42). In that study, the absolute eosinophil count and CRP level, as well as IgE levels, were shown to have limitations as longitudinal biomarkers of disease activity or predictors of flare in EGPA, demonstrating the lack of biomarkers of disease activity in EGPA. Due to the formation of IgE/anti-IgE immune complexes, serum IgE levels can remain high during treatment with omalizumab (43), thus suggesting that IgE levels should not be used to monitor the therapeutic response. Because of the small number of patients in our study, we were not able to analyze precisely the factors predictive of omalizumab response. However, the characteristics of the patients who had a complete response to omalizumab were similar to those of the other patients, and the therapeutic response appeared to be independent of age, sex, ANCA positivity, the BVAS, CRP levels, and IgE levels.

In atopic asthma, the treatment response to omalizumab appears to differ according to the patient's baseline blood eosinophil count, with a high eosinophil count being predictive of treatment success (44). In our study population, the median eosinophil count at the time of initiation of omalizumab (490/mm³) was low, despite refractory and/or relapsing disease, but most probably was attributable to high doses of concomitant prednisone. In addition, a previous study from the French Vasculitis Study Group (FVSG) showed that a low eosinophil count was the main predictive factor associated with relapse in a cohort of 383 EGPA patients (2), which was later confirmed prospectively (41). These findings suggest that our study population with low baseline eosinophil counts was probably at higher risk of EGPA relapse and omalizumab failure. Thus, this could be an explanation for the low complete response rate observed. Evidently, omalizumab needs to be further investigated in patients who had higher eosinophil counts at the time of treatment initiation.

Omalizumab appeared to be safe and well tolerated in the majority of our patients. No severe adverse event was reported in association with >375 injections of this biologic agent. Adverse events were mild and self-limited; 1 adverse event required treatment discontinuation, but there was no evidence of drug causality. These findings are consistent with those of other studies regarding the safety profile of omalizumab in asthma (45). However, a quarter of our population experienced disease relapse during omalizumab therapy that led to treatment discontinuation. Two patients experienced severe asthma flares, and 2 others developed retrobulbar optic neuritis suggestive of EGPA relapses. To our knowledge, some neurologic and ocular manifestations in patients with EGPA have been previously reported, such as ischemic optic neuropathy, cranial nerve palsy, or retrobulbar optic neuritis (46–52). In our patients, these manifestations were considered to be related to disease relapse and not directly induced by omalizumab, but an omalizumab-related adverse event cannot be excluded. These findings raise the question of whether omalizumab should be used in patients with EGPA, given its partial efficacy and the potential risk of relapse. After analysis of the benefit/risk ratio, however, omalizumab might be considered as an alternative therapeutic agent, but this will need to be reevaluated in comparison with future agents, especially anti-IL-5 monoclonal antibodies.

Our study has several limitations. First, the retrospective design was associated with some missing data and difficulty in assessing disease activity. Second, most patients received other medications in combination with

omalizumab, and there was no control arm, which limits the interpretation of outcomes. However, all but 1 patient had no modification of background immunosuppressive treatment while receiving treatment with omalizumab, thus allowing an estimation of efficacy. Third, our population appears to be heterogeneous, given the heterogeneity of the patients' clinical presentation and the discrepancies in therapeutic management between centers over time. However, this tends to decrease with harmonization of management within the FVSG.

In conclusion, this is the largest series in which the relationship between EGPA and omalizumab treatment was examined. Because no prospective clinical trial assessing omalizumab in EGPA is forthcoming as yet, our study provides useful data to physicians providing care. Our results suggest that in EGPA patients with asthmatic and/or sinonasal manifestations, omalizumab has mild efficacy for the treatment of asthma and/or ENT symptoms and may have corticosteroid-sparing effects in these patients. However, the risk of severe EGPA flares in treated patients, possibly due to the reduction in corticosteroid doses, raises the question of whether it should be used for the treatment of EGPA. After the risk/benefit ratio has been analyzed, however, omalizumab could represent an alternative therapeutic agent.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terrier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jachiet, Samson, Le Guenno, Devilliers, Le Jeunne, Mouthon, Guillevin, Terrier.

Acquisition of data. Jachiet, Samson, Cottin, Kahn, Le Guenno, Bonniaud, Devilliers, Bouillet, Gondouin, Makhoulouf, Meaux-Ruault, Gil, Bienvenu, Coste, Groh, Giraud, Dominique, Godeau, Puéchal, Khouatra, Ruivard, Mouthon, Terrier.

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Reply

To the Editor:

We thank Dr. Curtis et al and Dr. Pincus et al for their careful attention to our recent publication, and we share their interest in furthering the best possible understanding of the findings from the AMPLE trial (1).

Curtis and colleagues, in their lengthy letter, provide a fair summary of the findings contained in our brief report, which was descriptive in nature. However, we respectfully disagree with some of their observations. MBDA testing was performed on all patients for whom collected serum was available; we reported the correlations for all patients in whom both MBDA testing and traditional RA clinical outcome measures were available. We agree with Curtis et al that the cut points available for the DAS28-CRP analysis (2) are problematic, which is why we performed similar analyses across several other disease measures (i.e., CDAI, SDAI, RAPID3) (3–5) and encountered the same lack of correlation between these and the MBDA test. We did not perform statistical testing as we

believed this was inappropriate in a post hoc analysis, and interpreting the statistical analysis would be problematic. The purpose of our report was to determine, in this population and in this study with these 2 medications, abatacept and adalimumab, whether the MBDA test correlates strongly with clinical disease measure changes or radiographic progression—we found that it does not.

Curtis and colleagues' description of our published analysis of the relationship between the radiographic outcomes and the MBDA score in Figures 2C and D of our report is correct. We agree that analysis of the relationship between radiographic outcomes (e.g., nonprogressor rates) and the MBDA score could have been done in multiple ways, each of which could inform on different aspects of the correlation between these 2 outcome measures in patients with RA. Curtis et al describe one such alternative analysis: the correlation between radiographic progressors and MBDA scores, rather than non-progressors as we did. In the clinic, it is difficult to ascertain radiographic progressor status so it is therefore not practical; the use of a validated biomarker with high correlation with radiographic progression would be a very welcome addition to our clinical measures. We performed the analysis in question for this very reason—we were interested in the correlation (and strength of correlation) between a biomarker (the MBDA score) and clinical and radiographic outcomes. We chose radiographic nonprogression because it is an important patient-level assessment of response to therapy, and radiographic nonprogression was far more common than progression in AMPLE trial patients with either medication at both year 1 and year 2 (1,6).

The assumptions used by Curtis et al for “missing data” and progressor rates (i.e., number of patients, “overall 8 of 189 in the abatacept arm, 4 of 190 in the adalimumab arm”) to perform progressor analysis at year 1 (Figure 1 in their letter) are not accurate, but understandably so. The data used in Figure 2D of our article, for both year 1 and year 2, are contained in Supplementary Table 5, which does not contain the MBDA score results for radiographic progressors. Table 1 herein does show the distribution for both radiographic nonprogressors and progressors by MBDA score and treatment group for both year 1 and year 2.

Table 1. MBDA-defined disease activity in the RA patients by radiographic status at years 1 and 2*

Visit time point, MBDA-defined disease activity	Subcutaneous abatacept (n = 181)		Subcutaneous adalimumab (n = 186)	
	Radiographic nonprogressors	Radiographic progressors	Radiographic nonprogressors	Radiographic progressors
Year 1				
n	162	19	165	21
LDA	38 (23.5)	1 (5.3)	43 (26.1)	2 (9.5)
MDA	57 (35.2)	3 (15.8)	84 (50.9)	7 (33.3)
HDA	67 (41.4)	15 (78.9)	38 (23.0)	12 (57.1)
Year 2				
n	103	24	109	18
LDA	25 (24.3)	1 (4.2)	26 (23.9)	5 (27.8)
MDA	41 (39.8)	11 (45.8)	46 (42.2)	5 (27.8)
HDA	37 (35.9)	12 (50.0)	37 (33.9)	8 (44.4)

* Data are for all randomized and treated patients with MBDA scores and radiographs available. Values are the number (%). MBDA = multi-biomarker disease activity; RA = rheumatoid arthritis; LDA = low disease activity; MDA = moderate disease activity; HDA = high disease activity.

As Curtis and colleagues point out, when evaluating only patients with radiographic progression at year 1, most were found to have MBDA scores in the high disease activity (HDA) range (abatacept 78.9% [15 of 19]; adalimumab 57.1% [12 of 21]). Importantly, and especially since RA is a chronic disease, at year 2, the correlation between radiographic progression and an HDA MBDA score was much less striking (abatacept versus adalimumab 50% [12 of 24] versus 44.4% [8 of 18]). Of major importance, however, is that the year 1 findings evaluating progressors do not nullify our observation that for nonprogressors, the MBDA test results at years 1 and 2 did not correctly identify most patients' radiographic status. Most patients with an HDA score were nonprogressors at both year 1 and year 2 (abatacept versus adalimumab 81.7% versus 76% year 1 and 75.5% versus 82.2% year 2), meaning an HDA score in this study did not reliably distinguish between radiographic progressors and nonprogressors for patients with RA treated over 2 years with either abatacept or adalimumab on background methotrexate. We also found that a low disease activity (LDA) score did not correlate well with nonprogression as asserted by Curtis et al (Table 1 herein). Thus, in clinical practice, based on the results of our analysis, the utility of the MBDA score with respect to determining the likelihood of radiographic progression is much less than satisfactory, as there are many patients with an HDA score who do not progress radiographically and many with an LDA score who do progress.

We fully agree with Pincus and colleagues and their assessment of the importance of clinical disease activity measures in RA that can be relied upon when making treatment decisions. It is still important to evaluate the whole patient with a careful history and physical examination, as well as assessment of laboratory and imaging parameters. Composite clinical measures remain the gold standard for therapeutic decisions in RA. A patient-reported clinical measure, such as the RAPID3, could be considered when deciding to initiate, change, or discontinue therapy.

In addition to the primary objectives of assessing the relative safety and efficacy of the use of abatacept or adalimumab on background methotrexate, the AMPLE trial was designed to serve as a platform to explore biomarker-related analyses that could help further our understanding of the therapeutic interventions and clinical responses seen in a prospective head-to-head trial. In the absence of a clear understanding of which are the most relevant biomarkers to consider, we have looked at multiple types of biomarker analyses that could be useful in this endeavor; this included the MBDA test. We concur with the accompanying editorial published in the same issue of *Arthritis & Rheumatology* that encourages further efforts in this area (7), as there is a need to develop clinically relevant tools both for patients with RA and for clinicians. We look forward to the results of these efforts.

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The role of omalizumab in patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss): comment on the article by Jachiet et al

To the Editor:

We read with interest the report by Jachiet et al providing evidence that anti-IgE (omalizumab) therapy may have a glucocorticoid-sparing effect in eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) with asthmatic and/or sinonasal manifestations (1). In a nationwide (France) retrospective study, the authors evaluated 17 EGPA patients who received omalizumab in combination with other medications (glucocorticoids, azathioprine, cyclophosphamide, etc.) for severe steroid-dependent asthma and/or sinonasal involvement. Data on outcome variables (Birmingham Vasculitis Activity Score [BVAS] [2], prednisone dosage, eosinophil count, forced

expiratory volume in 1 second [FEV₁] [% predicted], FEV₁/forced vital capacity [% predicted], C-reactive protein level, and number of exacerbations per month) were collected every 3 months during 12 months of treatment; the median follow-up period was 22 months. The authors reported significant reduction of the prednisone dosage at each treatment time point compared with baseline, whereas no significant differences were noted for eosinophil count, BVAS, and FEV₁. Omalizumab was discontinued in 8 of 17 patients (due to disease remission [1 patient], adverse event despite disease remission, not related to omalizumab administration [1 patient], refractory disease [2 patients], and disease relapse [4 patients]). Omalizumab was well tolerated, and no serious adverse events were observed.

We would like to respectfully note that the results of a similar observational study were published by our group last year (3). In that report we described long-term (36-month follow-up) effects of omalizumab in 5 patients with EGPA and severe asthma who were seen at the Division of Clinical Immunology and Allergy, University of Naples Federico II. In our observational study, patients were treated with omalizumab (300–600 mg subcutaneously every 2–4 weeks) as add-on therapy to prednisone, inhaled glucocorticoids, and bronchodilators. At baseline and during omalizumab treatment, Asthma Control Test (ACT) results (4), eosinophil count, FEV₁ (% predicted), and prednisone dosage were recorded every 6 months. During omalizumab treatment, the FEV₁ rapidly and significantly increased and the ACT score progressively and significantly improved. Interestingly, eosinophilia decreased significantly, and oral prednisone treatment was discontinued in 1 of the 5 patients, and the dosage progressively reduced in another. Patients were also evaluated for dermatologic, cardiologic, renal, and neurologic involvement; all remained

clinically stable. As in Jachiet and colleagues' study, there were no adverse events related to omalizumab treatment.

There are similarities and differences between the 2 observational studies (Table 1). The study by Jachiet et al was a multicenter nationwide retrospective study on 17 patients whereas ours was a single-center prospective study on 5 patients. In the former study the characteristics of omalizumab treatment in terms of duration and number of administrations were variable. In contrast, in our patients omalizumab treatment was maintained throughout the 36 months of observation. In addition, some of Jachiet and colleagues' patients received immunosuppressive treatment while receiving omalizumab, whereas all patients in our study had received immunosuppressive therapy (cyclophosphamide or azathioprine) before, but not during, omalizumab treatment.

There are also some differences in clinical outcomes between the 2 studies. In our study, 2 parameters of asthma control (FEV₁ and ACT score) significantly improved, whereas FEV₁ did not change in the study by Jachiet et al (ACT score not evaluated). The eosinophil count significantly decreased (at the 24-month time point only) in our study whereas it did not change in the study by Jachiet et al. In both studies the prednisone dosage was progressively reduced, with the reduction reaching significance only in Jachiet et al's study. Jachiet and colleagues found no significant effect of omalizumab on the BVAS score, nor did we (data not shown in ref. (3)). Interestingly, we found that the urticarial lesions observed in 1 patient rapidly disappeared after the first administration of omalizumab, whereas Jachiet and colleagues reported that omalizumab had no effect in 2 patients with cutaneous involvement (urticarial and pruritic). Our observation is consistent with the previously reported finding that omalizumab

Table 1. Characteristics and findings of the 2 studies of omalizumab treatment in patients with EGPA*

	Jachiet et al (ref. 1)	Detoraki et al (ref. 3)
Study design	Observational, retrospective, multicenter	Observational, prospective, single-center
No. of patients	17	5
Age, years	18–87	40–68
Total IgE	28–7,503 IU/ml	228–1,500 KU/liter
Baseline eosinophil count, per mm ³	0–2,230	320–2,500
ANCA positive	5/17	1/5
Baseline BVAS	0–8 (median 2.5)	Low†
Omalizumab combined with corticosteroid	17/17	4/5
Omalizumab combined with immunosuppressive agent	8/17	0/5
Duration of omalizumab treatment, weeks	1–216 (median 64)	144 (36 months)
Discontinuation of omalizumab	8/17	0/5
Effect of omalizumab on BVAS	Reduction (NS)	No increase†
Effect of omalizumab on daily prednisone dosage	Statistically significant reduction	Reduction (NS)
Effect of omalizumab on eosinophil count	Increase	Reduction (statistically significant at 24 months)
Effect of omalizumab on ACT score	Not evaluated	Statistically significant increase
Effect of omalizumab on FEV ₁	Slight increase (NS)	Statistically significant increase
Effect of omalizumab on cutaneous manifestations (urticaria, pruritus)	No effect	Resolution
EGPA relapse	4/17	0/5

* EGPA = eosinophilic granulomatosis with polyangiitis (Churg-Strauss); ANCA = antineutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; NS = not significant; ACT = Asthma Control Test; FEV₁ = forced expiratory volume in 1 second.

† Not reported in article.

rapidly improves skin lesions in patients with chronic spontaneous urticaria (5). We would like to emphasize the above findings because the results of our study, which represented the largest reported cohort of EGPA patients treated with omalizumab for a long period of time (36 months), were not discussed in the report by Jachiet et al.

The results presented by Jachiet et al and by our group extend the findings described in previous case reports on the short-term efficacy of omalizumab in adults (6,7) and pediatric EGPA patients (8). To date, no randomized controlled interventional trials in EGPA have been published. Therefore, treatment decisions are based on expert opinion, small pilot studies, or extrapolation from efficacious immunosuppressive therapies in other types of vasculitis (9,10). Given the role of eosinophils in EGPA (11), the anti-interleukin-5 monoclonal antibody mepolizumab has been used, with limited success, in a few adult EGPA patients (12–14).

The heterogeneous clinical and genetic spectrum of EGPA (15,16) makes the treatment of this vasculitis particularly challenging. A better characterization of different phenotypes and/or genotypes of the disease might provide the basis for efficacious targeted therapy with monoclonal antibodies.

EGPA is considered a Th2-driven vasculitis associated with increased levels of serum IgE (3) and IgE-containing immune complexes (17). Ligelizumab is a novel anti-IgE monoclonal antibody with greater efficacy than omalizumab in patients with allergic asthma (18). Although the open-label design of the studies by Jachiet et al and by our group is associated with potential bias, both studies suggest that omalizumab may have a glucocorticoid-sparing effect in adult EGPA patients with asthmatic and/or sinonasal symptoms. The efficacy and safety of omalizumab and/or ligelizumab in EGPA should be assessed in double-blind randomized placebo-controlled trials.

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Biologic therapy for eosinophilic granulomatosis with polyangiitis (Churg-Strauss): comment on the article by Jachiet et al

To the Editor:

Over the last decade, biologic agents have become an important component of therapy for systemic vasculitides, e.g., rituximab for granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis, or tocilizumab for giant cell arteritis. However, a risk/benefit ratio of biologic therapy for eosin-

ophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) has not been well studied. Jachiet et al have reported results of a retrospective study of treatment with omalizumab (an anti-IgE monoclonal antibody) in 17 patients with refractory and/or relapsing EGPA and severe steroid-dependent asthma and/or sinonasal involvement (1). Treatment response was defined as improvement of asthma and/or ear/nose/throat (ENT) exacerbations. Therefore, this was an “asthma” study rather than a “vasculitis” study, and efficacy of omalizumab in vasculitis remains unclear. Notably, 7 patients described in Jachiet and colleagues’ report had other signs and symptoms (skin disease, myalgia, arthralgia, pulmonary infiltrates) in addition to asthma and/or ENT involvement. Following treatment, these relatively mild manifestations of active vasculitis had improved significantly in only 3 patients. Thus, omalizumab does not appear to be a promising agent for management of vasculitis. Moreover, treatment with omalizumab may result in manifestation of other disease features due to steroid tapering: 2 of the patients in Jachiet et al’s study developed retrobulbar optic neuritis related to disease relapse. Unlike GPA, severe eye disease is a rare finding in EGPA; therefore, this high incidence (~12%) of retrobulbar optic neuritis in patients treated with omalizumab would not have been expected.

It has previously been suggested that clinical vasculitis manifestations, such as peripheral neuropathy or renal involvement, occur more frequently in patients with antineutrophil cytoplasmic antibody (ANCA)-positive EGPA than those with ANCA-negative disease (2). It can be speculated that the risk/benefit ratio of omalizumab may be more favorable in patients with ANCA-negative EGPA. Jachiet et al did not report the ANCA status of patients with vasculitis relapse, though they stated in the Discussion that response to omalizumab seemed to be independent of ANCA positivity.

Omalizumab induced a complete or partial response (i.e., absence of asthma and/or ENT exacerbations) in 65% of patients. However, the moderate reduction in prednisone dosage following biologic therapy raises a question as to whether the same effect could have been achieved by intensification of treatment with inhaled corticosteroids and/or long-acting bronchodilators. Jachiet et al did not present data on concomitant use of antiasthmatic medications (this information was likely not available given the retrospective design of the study). Recently, Detoraki et al reported on 5 patients with EGPA and moderate-to-severe asthma who were treated with omalizumab as add-on therapy to prednisone, inhaled corticosteroids, and bronchodilators (3). Over a treatment period of 36 months, omalizumab was found to be safe and enabled corticosteroid tapering while reducing eosinophilia and improving asthma symptoms. Although the steroid-sparing effect of omalizumab is apparently beneficial, it should not be overestimated. In a Cochrane systematic review, a significant benefit of subcutaneous omalizumab versus placebo was noted with regard to reduction in the frequency of hospitalization or discontinuation of inhaled corticosteroids in patients with bronchial asthma (4). However, there was no significant difference between omalizumab and placebo groups in the proportion of participants who were able to discontinue oral corticosteroid therapy.

Unlike omalizumab, rituximab (an anti-CD20 monoclonal antibody) has no antiasthmatic activity and is being used to treat relapsing and/or refractory vasculitis. Mohammad et al have reported on 41 patients with EGPA treated with rituximab in 4 centers (5). At 6 months and 12 months, respectively, remission or partial response was achieved in 83% and 87% of

patients. In our own series, complete or partial remission was achieved following rituximab administration in all 6 patients with moderately severe or severe relapsing EGPA that was refractory to conventional immunosuppression (6). Notably, in 2 patients, attempts to reduce the dosage of or discontinue corticosteroids led to a minor relapse that required intensification of treatment (increase in corticosteroid dosage or addition of mycophenolate mofetil), while 1 patient developed severe bronchospasm following rituximab infusion. Therefore, along with infections, the risk of aggravating asthma during rituximab infusion should be taken into account.

Mepolizumab (an anti-interleukin-5 monoclonal antibody) is another promising biologic treatment for EGPA. Its efficacy in patients with refractory, relapsing, or steroid-dependent EGPA manifestations was preliminarily shown in small open-label studies (7,8) and is currently under investigation in a randomized clinical trial (MIRRA; ClinicalTrials.gov: NCT00527566). Mepolizumab may have advantages over omalizumab and rituximab, as it seems to be effective in both vasculitis and eosinophilic asthma.

In conclusion, Jachiet et al have provided important data for rheumatologists caring for patients with EGPA. Regrettably, the future of omalizumab in EGPA does not look bright. Therefore, we should focus on other biologic agents that would ideally have activity against both vasculitis and asthmatic/sinonasal manifestations of EGPA.

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Reply*To the Editor:*

We would like to thank Dr. Detoraki et al and Drs. Novikov and Moiseev for their interesting comments regarding our study on anti-IgE (omalizumab) therapy in patients with refractory and/or relapsing EGPA.

First, we apologize for not mentioning the report by Detoraki et al describing the effects of omalizumab in 5 patients with EGPA and severe asthma (1). We acknowledge that there was variability among our study patients in terms of duration of omalizumab treatment, number of administrations, and concomitant therapy. This heterogeneity was due to the multicenter design of the study and the off-label use of omalizumab in refractory EGPA, a particularly difficult condition to manage. Refractory disease often requires add-on immunosuppressive agents, as in the study by Kim et al on adjunct therapy with mepolizumab in patients with EGPA (2).

We agree that our study demonstrated partial efficacy only in severe and high-dose steroid-dependent asthma and sinonasal involvement rather than for vasculitis manifestations; the latter were never the indication for initiation of omalizumab. These manifestations, sharing common pathophysiologic features with eosinophilic disorders and asthma, were more likely to respond to specific targeting therapy (3,4).

Novikov and Moiseev raise concerns regarding positive or negative ANCA status and omalizumab response. ANCA-positive patients are prone to develop vasculitic manifestations of the disease, i.e., glomerulonephritis and peripheral neuropathy, whereas ANCA-negative patients have more frequent cardiac manifestations (5). In our study, 12 EGPA patients (71%) were ANCA negative and 5 (29%) were ANCA positive (with enzyme-linked immunosorbent assay-detected antibodies to myeloperoxidase in 4 patients, and no specificity in 1 patient). Among the 12 ANCA-negative patients, complete response was achieved in 3 (25%) and partial response in 5 (42%); 4 patients (33%) had no improvement. Among the 5 ANCA-positive patients, complete response was achieved in 3 (60%), and 2 (40%) had no improvement.

Finally, despite its limitations, our study is the largest evaluation of omalizumab in refractory and/or relapsing EGPA

published to date, and the findings suggest a potential, though moderate, corticosteroid-sparing effect. Because of the questionable risk/benefit ratio in our patients (which should be interpreted with caution due to the small study sample), the use of omalizumab in EGPA will probably be restricted to very selected patients. Therapeutic management of EGPA remains challenging, and clinicians should balance the strengths and limitations of the available data and individual patient characteristics before deciding on the best treatment. While it is challenging to conduct randomized placebo-controlled trials in rare diseases such as EGPA, further studies should focus on deciphering this complex disease and evaluating appropriate biologic agents to obtain useful data for clinicians providing care.

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