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ORIGINAL ARTICLE

Omalizumab in patients with eosinophilic granulomatosis with polyangiitis: a 36-month follow-up study

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Abstract

Objective: Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis characterized by asthma and blood eosinophilia, with the lung being the organ most frequently affected. Oral glucocorticoids and/or immunosuppressive drugs are the mainstay therapy of EGPA. Occasional reports suggest that EGPA patients can be treated with omalizumab in addition to conventional therapy to achieve asthma control. To investigate the long-term effects of omalizumab in patients with EGPA and asthma (2 females, 3 males, age 41–64 years), we carried out a 36-month follow-up observational study. At the time of enrollment, the patients were on maintenance therapy and had moderate to severe allergic asthma, eosinophilia and rhinosinusitis. Mononeuropathy/polyneuropathy and/or histological evidence of tissue eosinophilic infiltration were also present. **Methods:** Patients were treated with omalizumab (300–600 mg s.c. every 2–4 weeks) as add-on therapy to prednisone, inhaled steroids and bronchodilators. During omalizumab treatment, spirometry, the asthma control test (ACT) score and eosinophilia were evaluated, and prednisone dosage was recorded. **Results:** During the 36 months of omalizumab treatment asthma progressively improved as indicated by spirometry and the ACT score. Eosinophilia progressively decreased. The oral prednisone dose was reduced or withdrawn during treatment. No adverse events were recorded. **Conclusions:** In patients with EGPA and moderate to severe allergic asthma, omalizumab can be beneficial and safe. It enables corticosteroid tapering while decreasing eosinophilia and improving asthma symptoms over 36 months.

Keywords

Case reports, control/management, morbidity and mortality, pharmacotherapy, therapy

History

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a small vessel vasculitis occurring in patients with asthma and with blood and tissue eosinophilia [1,2]. The most frequently involved organ is the lung followed by the skin. EGPA, however, can affect any organ system of the body [1–3]. It is a rare disease with an annual incidence of 0.5–4.2 cases/10⁶ inhabitants [4] and a prevalence of 11–14 cases/10⁶ inhabitants [5,6]. The incidence among asthmatics is approximately 35–64 cases/10⁶ person-years [7]. The disease usually arises in subjects aged 40–60 years [8], whereas childhood cases are rare [9]. There is no evidence of gender predominance, familial clustering or ethnic predisposition [10].

Immunogenetic factors such as HLA-DRB4 may confer susceptibility to EGPA, whereas exogenous factors (environmental agents and drugs) are thought to trigger the disease [11]. Although EGPA pathogenesis is incompletely understood, it is

considered a Th2-mediated disorder. In fact, Th-2 associated cytokines (IL-4, IL-13 and IL-5) seem to be up-regulated in active EGPA [12,13]. Blood and tissue eosinophilia are characteristics of the disease, which is driven in part by eotaxin-3 produced by epithelial and endothelial cells [1,14]. Also, the B-cell response may contribute to EGPA pathogenesis given the findings that increased IgE levels are common in EGPA and that the B-cell depleting agent rituximab produced promising results in patients with refractory EGPA [15,16].

Primary therapy of EGPA is systemic glucocorticoids, in combination with immunosuppressive drugs (e.g. cyclophosphamide) [11]. Newer “targeted” approaches are rituximab [15,16] and the IL-5-neutralizing antibody mepolizumab [3,17,18]. These drugs and biologics have relevant side effects and are not effective in all patients. EGPA remains a challenge for clinicians because current treatments based on glucocorticoids and immunomodulators do not always induce remission and are associated with significant side effects and morbidity. Consequently, alternative strategies for EGPA patients are needed.

The anti-human IgE monoclonal antibody omalizumab is effective in patients with moderate to severe allergic asthma [19,20]. There is evidence that omalizumab treatment

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decreases blood eosinophils [21] and reduces eosinophil count in the airways and in the sputum of asthmatics [22]. The mechanism of eosinophil reduction by anti-IgE remains unclear, although a direct interaction with the IgE receptor on eosinophils might be a contributing factor [23]. Omalizumab can increase eosinophil apoptosis presumably by down-regulating eosinophil growth-survival factors (e.g. IL-5, GM-CSF) [21,23]. Given the effect of omalizumab on eosinophilic reduction a short-term treatment with omalizumab has been tried in some adult [24–27] and pediatric EGPA patients [28]. The long-term safety and efficacy of omalizumab in EGPA patients have not yet been evaluated even in observational studies.

The purpose of this study was to evaluate prospectively the safety and efficacy of omalizumab over a period of 36 months in five patients with EGPA and moderate to severe allergic asthma.

Case study

Five patients (2 females, 3 males) aged 41–64 years with EGPA were recruited at the Clinical Research Center for Clinical Immunology and Allergy of the University of Naples Federico II between July 2010 and September 2011. Patients' characteristics at baseline (T0) were: moderate-severe allergic asthma [FEV₁ 68.5 ± 2.7%, mean asthma control test (ACT) score 11 ± 0.7]; eosinophilia (1148 ± 382 cells/μl) and rhinosinusitis and/or nasal polyps. All patients were atopic (Table 1). Asthma severity was assessed according to GINA guidelines [19]. Systemic vasculitis activity was assessed using the Birmingham Vasculitis Activity Score (BVAS) [29].

Lung involvement was considered when ground glass opacity or consolidation areas associated with bronchial wall thickening and small centrilobular nodules or pleural effusion were evident upon high resolution computer tomography. Heart involvement, a well-known adverse prognostic factor, was considered in the case of EKG abnormalities or cardiac echocardiography abnormalities (impaired cardiac function, intra-cardiac thrombus formation). Mononeuropathy/polyneuropathy was evaluated by electromyography and clinical examination and was present in three patients. Skin involvement was defined as the presence of urticaria, livedo or ulcer; one patient was affected by urticarial vasculitis documented by skin biopsy. Gastrointestinal involvement was indicated by the presence of symptoms of epigastralgia, abdominal pain, diarrhea or positive endoscopic signs. One of the five patients was a smoker.

At baseline (T0), four patients were receiving prednisone *per os* (T0 mean value 22.5 ± 10.1 mg/die); one patient started omalizumab therapy while in clinical remission of EGPA 3 months after stopping oral glucocorticoid therapy. All patients were receiving therapy with inhaled long-acting β₂ agonists and inhaled steroids for at least 6 months at constant doses. Inflammatory markers (ESR, PCR and fibrinogen) and oncologic markers (α-fetoprotein, CA 19-9, CA 15-3, CA 125, PSA, β₂-microglobulin), kidney (blood urea nitrogen and creatinine) and liver function tests (transaminases, alkaline phosphatase, total bilirubin, lactate dehydrogenase) were evaluated every 6 months in all patients. Safety was evaluated by recording and monitoring the frequency and severity of adverse events (malignancies, urticaria,

Table 1. Patients' characteristics at baseline (T0).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	46	68	63	41	40
Sex	F	M	M	M	F
Total IgE (kU/l)	1078	948	153	1500	228
Body weight (kg)	52	70	93	79	65
Omaliuzumab dose and frequency	450 mg/2 weeks	600 mg/2 weeks	300 mg/4 weeks	600 mg/2 weeks	300 mg/4 weeks
Rhinosynusitis	+	+	+	+	+
Nasal polyposis	–	+	–	–	–
Urticarial vasculitis	+	–	–	–	–
Neuropathy	+	+	+	–	–
Oral prednisone (mg/die)	5	0	50	25	10
LABA+ICI (μg/die)					
Eosinophils (μl)	1430	680	320	2500	810
MPO-ANCA	+	–	–	–	–
ACT score (min 0–max 25)	12	10	9	11	13
	Budesonide/formoterol 640/18	Budesonide/formoterol 640/18	Fluticasone/salmoterol 1000/100	Ciclesonide/formoterol 320/9	Fluticasone/salmoterol 1000/100

Patients 1 and 5: positive skin prick tests for Dust Mites (*Dermatophagoides pteronyssinus* and *farinae*) and pollens (*Graminaceae*). Patients 2 and 3: positive skin prick test for pollens (*Parietaria judaica*, *Parietaria officinalis* and Olive tree). Patient 4: positive skin prick test for Dust Mites (*Dermatophagoides pteronyssinus* and *farinae*) and Alternaria.

hypersensitivity reactions, injection-site reactions, bleeding-related events and thromboembolic events).

The inclusion criterion was a diagnosis of EGPA as defined by the American College of Rheumatology [30]. The 2012 Chapel Consensus Conference for the nomenclature of vasculitis [2] was introduced after the initiation of our study. All patients had previously received immunosuppressive therapy (cyclophosphamide or azathioprine) and/or glucocorticoids. Four patients were maintained on a stable dose of prednisone (Table 1). Exclusion criteria were non-EGPA hypereosinophilic syndromes, non-EGPA-ANCA-associated vasculitis and malignancy. Pregnant or nursing patients were excluded.

During the initial screening phase patients provided signed informed consent to the study, and their medical history was reviewed by at least two physicians who had confirmed the diagnosis of EGPA based on clinical history and medical records [30]. Patients underwent physical examination, spirometry test [31] was performed using a Quark SPIRO (COSMED) Spirometer (Rome, Italy) according to the standards of the American Thoracic Society [30]. Forced Expiratory Volume at 1 sec (FEV_1) was evaluated. The highest value of three technically satisfactory attempts was recorded. The ACT questionnaire, a validated five-item, patient-completed measure of asthma control [32], was administered to all patients. Blood samples were collected to determine serum total IgE and blood eosinophilia.

Peripheral blood eosinophils were counted with a Beckman Coulter LH 750 Analyzer (Milan, Italy). Total IgE was determined by Phadia 250. All measurements including prednisone dosage and tapering were recorded at T0 and 6, 12, 18, 24 and 36 months thereafter.

Patients were treated with omalizumab (300–600 mg s.c. every 2–4 weeks) as add-on therapy to prednisone, inhaled steroids and bronchodilators. Omalizumab dosage and frequency of dosing were based on serum total IgE level (kU/L) and body weight (kg), according to the manufacturers' recommendations. For patient 4 (total IgE 1500 kU/L, body weight 79 kg), we administered 600 mg of omalizumab every 2 weeks (Table 1).

Statistical analysis

Variations in FEV_1 , ACT score, eosinophil count and prednisone dosage were compared by repeated measures ANOVA followed by Newman–Keuls. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Graph-pad PRISM.

Results

Patients treated with omalizumab showed an improvement in FEV_1 after 6 months of treatment (T0: $68.5 \pm 2.7\%$ versus T6: $93 \pm 3\%$; $p < 0.05$) which was maintained throughout the 36 months of treatment (Figure 1A). The ACT score increased

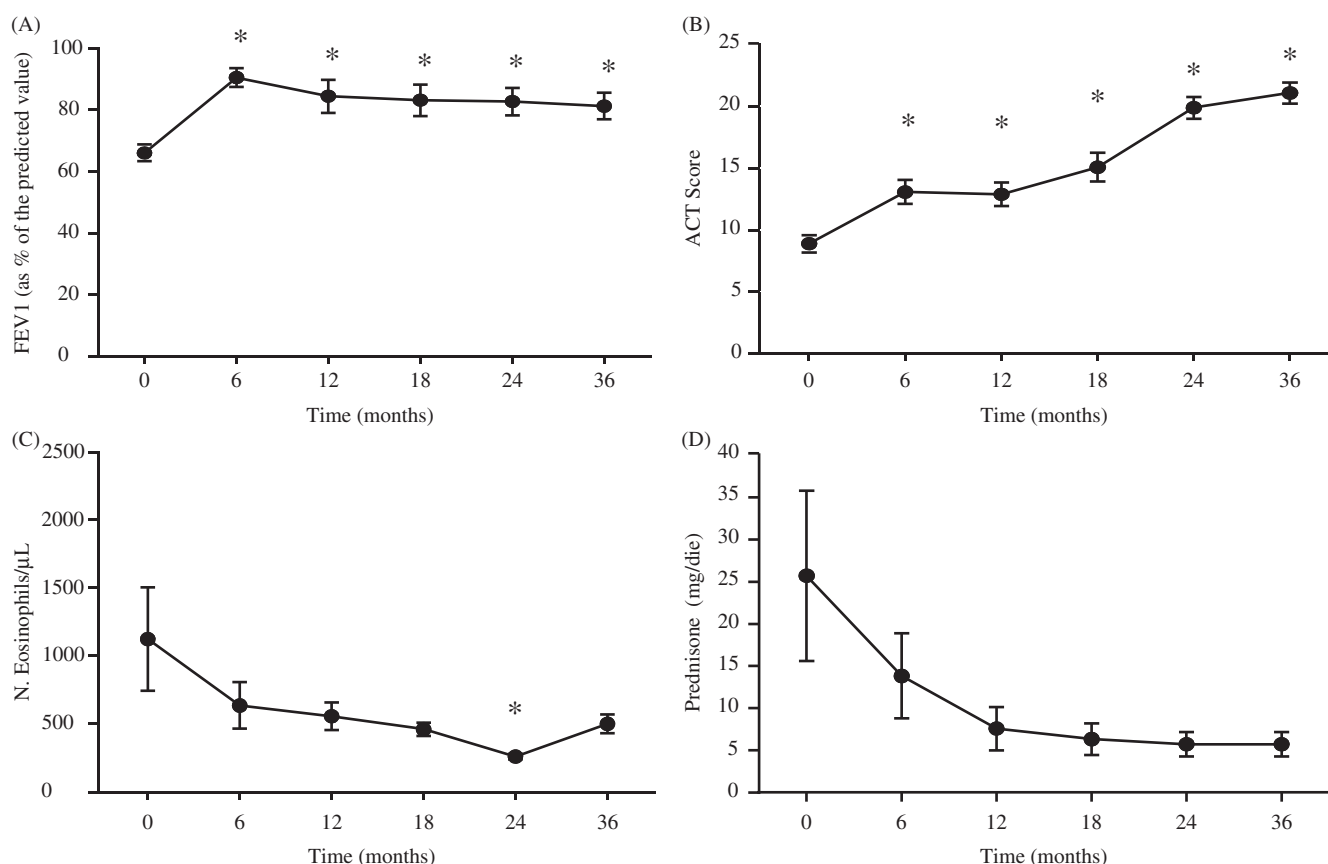


Figure 1. Effects of omalizumab on FEV_1 (A), ACT score (B), eosinophil count (C) and prednisone dosage (D) over 36 months of treatment in patients with EGPA (* $p < 0.05$ when compared to the value at time 0). The figure illustrates the data from five patients except in Figure D in which one patient was omitted because was not taking prednisone at T0.

after 6 months of treatment (T0: 11 ± 0.7 versus T6: 15.2 ± 0.9 ; $p < 0.05$) and progressively increased thereafter up to 36 months (Figure 1B). Eosinophil count decreased after 6 months of therapy, and was significantly lower than baseline after 24 months of therapy (T0: 1148 ± 382.5 cells/ μ l versus T24: 280 ± 20 cells/ μ l; $p < 0.05$) (Figure 1C). Despite the high doses of prednisone (up to 50 mg/day), asthma was not perfectly controlled at time T0 in four patients. Interestingly, the dose of prednisone progressively decreased from month 6 to the end of the study (Figure 1D). Prednisone was withdrawn in two patients after 12 months of treatment. One of the five patients did not need treatment with oral glucocorticoids even at T0. This patient is not included in Figure 1(D). The urticarial vasculitis lesions present in one patient for more than 2 years disappeared after the first administration of omalizumab and did not recur during the study.

Each year, patients were evaluated for dermatologic, cardiologic and neurologic involvement. All patients remained clinically stable; indeed, no worsening of respiratory, cutaneous, cardiologic or neurologic symptoms was recorded. Inflammatory and oncologic markers, kidney and liver function tests did not change during the treatment period (data not shown). No adverse events (i.e. anaphylaxis) occurred immediately after or greater than 2 h after administration of omalizumab.

Discussion

EGPA is characterized by systemic vasculitis, blood and tissue eosinophilia and a long-term history of asthma [1,2,33]. EGPA is a rare disease and therefore testing innovative treatments is challenging because only a small number of patients can undertake randomized placebo-controlled trials.

This observational study suggests that omalizumab decreases asthma activity and improves pulmonary function in EGPA patients. Omalizumab treatment was associated with a rapid and steady improvement in lung function (FEV₁) and a progressive increase in ACT score during the 36 months of therapy. Furthermore, omalizumab allowed corticosteroid tapering, and thus functioned as a corticosteroid-sparing therapy. However, the decrease in corticosteroid dose was not statistically significant presumably due to the small number of patients evaluated in this study. Given the side effects of chronic glucocorticoid therapy (weight gain, increased risk of infection, adrenal suppression, osteoporosis, etc.) [34], corticosteroid tapering is a major clinical benefit of omalizumab treatment. Interestingly, the glucocorticoid reduction was paralleled by a decrease of blood eosinophils. During the observation period patients remained clinically stable from a dermatologic, cardiologic and neurologic point of view and no adverse events were recorded.

Infiltrating eosinophils in vasculitic lesions of EGPA and blood eosinophils correlate with the course of the disease, suggesting that these cells play a pathogenetic role [1,33,35]. Memory T cells in the vasculitic lesions increased T cell activation [36] and responsiveness of disease activity to treatment with suppressors of cellular immunity [37] suggest T-cell involvement in EGPA. T-cells from such patients show a Th2-like phenotype, with increased production of IL-4, IL-5

and IL-13 [12,13]. T-cell activation can induce up-regulation of cytokines/chemokines (e.g. IL-5, Rantes/eotaxins) responsible for eosinophilia and eosinophilic activation. Alternatively, the Th2-mediated response in EGPA may be secondary to eosinophil production of cytokines (e.g. IL-4, IL5) inducing Th2-like polarization. In both cases, eosinophilia is a central feature of EGPA and treatment targeted to decrease eosinophils could be beneficial.

According to current guidelines, omalizumab is a safe and effective add-on treatment in moderate to severe asthma [19,20,38–41]. This treatment can lead to better control of asthma by reducing exacerbations, dose of glucocorticoids and by improving quality of life [20,40]. Omalizumab binds with high affinity to the Cε3 domain of free IgE, thus preventing the interactions of IgE with the FcεRI expressed on mast cells, basophils, eosinophils and dendritic cells and blocking allergen-induced degranulation [42–44]. In asthmatic patients, higher IgE values are associated with more severe obstruction [45]. Omalizumab reduces free serum IgE and expression of the high affinity receptor FcεRI on effector cells [46,47]. Moreover, by inhibiting the binding of IgE to the trimeric complex FcεRI on dendritic cells [44,48], omalizumab can reduce the efficacy of antigen presentation to T lymphocytes.

The reduced T cell and mast cell/basophil activity might result in a decrease of Th2-like cytokines (e.g. IL-4, IL-5, IL-13), thus explaining the reduction of blood eosinophils. Omalizumab decreases eosinophils in blood, airways and sputum of asthmatic patients [21,22] presumably by a direct interaction with the IgE receptor on eosinophils [23] and/or by down-regulation of eosinophil growth-survival factors (e.g. IL-5, GM-CSF) [21,23]. Given the role of eosinophils in EGPA, the IL-5 neutralizing antibody mepolizumab has been evaluated in some patients with this disorder [3,17,18]. In a pilot study, 4 months of treatment with mepolizumab proved to be safe and enabled glucocorticoid tapering while maintaining clinical stability [3]. Although, as expected, anti-IL-5 reduced blood eosinophils, there was no improvement in lung function. Our results demonstrate that omalizumab, not only reduced eosinophilia, but also improved lung function in EGPA patients over a long period of time. The difference in the clinical effects between the two biologics presumably reflects the different mechanisms of action of mepolizumab and omalizumab. A limitation of our study is that we did not measure the cytokines/chemokines in the airways (bronchoalveolar lavage and/or sputum), and therefore the mechanism of eosinophil reduction by omalizumab remains unclear.

There is evidence that the B-cell response may also contribute to EGPA pathogenesis: rituximab, a B-cell depleting agent, proved to be an efficient and safe treatment for patients with refractory EGPA [15,16]. In a pilot study, rituximab has been administered to three EGPA patients with renal involvement, in a four weekly doses regimen, in addition to oral prednisone [15]. All patients achieved remission of the renal manifestations of their disease during the period of B-lymphocyte depletion. Thiel et al. treated nine EGPA patients for 3 months, obtaining a significant decrease of BVAS, blood eosinophils and prednisone dosage but a less positive impact on asthma symptoms. In all patients rituximab therapy was combined with a standard immunosuppressive

therapy (e.g. azathioprine, methotrexate) [16]. These results support the central pathogenetic role for B-lymphocytes in EGPA and reflect a different mechanism of action of rituximab compared to omalizumab.

Omalizumab has also been suspected of causing full-blown EGPA with development of systemic vasculitis that may affect the lung, gastrointestinal tract, and/or the skin or other organs. EGPA in these patients is subsequent to the diagnosis of allergic rhinosinusitis and asthma and occurs presumably consequently to glucocorticoid tapering [49,50].

Conclusion

The results of this 36-month follow-up study suggest that omalizumab may be clinically beneficial for EGPA patients; indeed, it improves asthma symptoms and lung function and enables glucocorticoid tapering while decreasing eosinophil count. These results extend the outcomes of previous case reports on the short-term efficacy of omalizumab in treating respiratory symptoms of eosinophilic vasculitic disorders [25–28]. We recognize that the open-label design of this study is associated with biases and that the small sample of patients makes it difficult to generalize our results to EGPA patients at large. The efficacy and safety of omalizumab in EGPA should be assessed in a larger, randomized, double-blinded placebo-controlled trial.

Declaration of interest

A declaration of interest statement reporting no conflict has been inserted. Please confirm the statement is accurate.

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