

Omalizumab in eosinophilic granulomatosis with polyangiitis: friend or foe? A systematic literature review

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ABSTRACT

Objective. To systematically evaluate, through a Medline search, the role of omalizumab in eosinophilic granulomatosis with polyangiitis (EGPA).

Methods. A systematic review was performed with the following inclusion criteria: original articles and case reports written in English and reporting an association between omalizumab and EGPA.

Results. We found 18 papers on EGPA (14 case reports, 3 retrospective cohort studies, 1 prospective cohort study). Omalizumab showed to be effective as corticosteroid-sparing agent in EGPA patients with severe asthmatic manifestations. On the contrary, conflicting results concerned its use in refractory forms of EGPA. Plausible is the increased risk of EGPA onset among asthmatic patients treated with omalizumab, probably related to steroid reduction, even if it cannot be excluded that omalizumab might be occasionally directly involved in the pathogenesis.

Conclusion. Our findings support the use of omalizumab in selected forms of EGPA, but caution in the tapering of corticosteroids is also recommended. Quality of evidence is limited, as the source of information was mainly case reports. Clinical trials are required in order to evaluate the role of omalizumab in EGPA and to ascertain the risk of asthmatic patients given omalizumab to develop EGPA.

Introduction

Omalizumab is a recombinant humanised anti-immunoglobulin E (IgE) monoclonal antibody which binds selectively to the Cε3 domain of the Fc fragment on the heavy chain of free IgE, thus preventing its interaction with the high-affinity and low-affinity IgE receptors found on the surface of mast cells, basophils, eosinophils and

B cells. Because the Cε3 domain mediates IgE binding with the α chain of IgE receptors, omalizumab interferes with IgE-FcεRI interaction, thereby preventing mast cell/basophil degranulation thus reducing the activation of inflammatory cells and the release of pro-inflammatory factors. In addition, omalizumab can block IgE-mediated antigen-presenting processes and inhibit Th2 amplification of inflammatory reactions (1).

Omalizumab was recently licensed as a therapy for patients aged 6 and older with allergic asthma, with a subcutaneous administration every 2 to 4 weeks, based on body weight and serum IgE levels (2). Several studies demonstrated a significantly greater improvement in asthma control in terms of inhaled glucocorticoids required, as well as in risk of exacerbation and hospitalisation, with an additional positive action on health-related quality of life (3). Similarly, real-life studies confirmed its effectiveness and safety in the treatment of chronic spontaneous urticaria (CSU), after the failure of first-line therapy, at the dosage of 150 mg either 300 mg every four weeks (2, 4).

How omalizumab works in asthma and CSU remains largely unclear. Studies have shown that omalizumab is able to determine eosinophil apoptosis and to down-regulate the production of inflammatory cytokines, thus exhibiting anti-allergic and anti-inflammatory properties (5). Omalizumab treatment has shown to be effective in several diseases such as aspirin-exacerbated respiratory disease (6), chronic eosinophilic pneumonia (7) and hypocomplementemic urticarial vasculitis syndrome (HUVS), a very rare small-vessel vasculitis of unknown aetiology often associated with systemic lupus erythematosus (SLE) (8). In this regard,

Competing interests: none declared.

omalizumab was effective in a milder form of HUVS, with prevalent skin and gastrointestinal involvement (9), whereas did not improve skin lesions in a severe form of HUVS with renal and pulmonary involvement (10).

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, characterised by necrotising vasculitis of the small to medium-sized vessels (11). The natural history of the disease usually includes a prodromal stage characterised by atopy, allergic rhinitis, and asthma, followed by an eosinophilic and a vasculitic stage. The withdrawal of corticosteroids in patients with asthma can act as a trigger leading to the systemic involvement of the disease. A patient can be classified as having EGPA if affected by at least four of the six following manifestations: (1) asthma; (2) eosinophilia > 10% (3) mononeuropathy (including multiplex) or polyneuropathy; (4) non-fixed pulmonary infiltrates; (5) paranasal sinus abnormality; and (6) the presence of extravascular eosinophils in a biopsy specimen. In addition, strongly elevated IgE and IgG4 levels are commonly observed in EGPA (12). Glucocorticoids with or without immunosuppressants and high-dose intravenous immunoglobulin therapy (IVIG) lead to successful remission in the majority of EGPA patients but is well-known that EGPA patients experience frequent relapses during glucocorticoid tapering. Long-term maintenance therapy with immunosuppressants is often used for preventing the relapse of EGPA but its efficacy is still controversial (13). Saku *et al.* recently found that azathioprine (AZA) maintenance therapy and high eosinophil counts at onset could represent independent factors for lower relapse risks, whereas high immunoglobulin E (IgE) levels at onset could be seen as a risk factor for relapses (14). As a matter of fact, the management of EGPA includes corticosteroids alone or in combination with conventional immunosuppressants (15). Since those agents are often ineffective in the control of chronic asthma and/or rhinosinusitis (the treatment of which requires long-term high-dose corticosteroids)

omalizumab has been tested in EGPA, with conflicting results.

The aim of our review was to systematically analyse the role of omalizumab in EGPA.

Methods

Literature search

A Medline search of English language articles published up to June 2019 in the PubMed database was performed with the following key words: omalizumab and vasculitis, omalizumab and small-vessel vasculitis, omalizumab and anti-neutrophil cytoplasmic antibodies (ANCA), omalizumab and eosinophilic granulomatosis with polyangiitis, omalizumab and Churg-Strauss syndrome.

Study selection

Duplicates were removed and all titles and abstracts resulting from the search strategy were reviewed to identify eligible papers. Afterwards full texts of the remaining studies were assessed. All articles eventually selected fulfilled the following eligibility criteria: original articles and case reports written in English and reporting an association between omalizumab and EGPA. Articles that did not meet these inclusion criteria were excluded. The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Results

A total of 94 articles were reviewed and, after selection, 18 papers on EGPA were included in the present review: 14 case reports, 3 retrospective cohort studies, 1 prospective cohort study. Since required diagnostic criteria for EGPA were not satisfied, we decided to exclude a dramatic case concerning a 75-year-old woman who, 81 months after the beginning of omalizumab, presented skin vasculitis, bilateral pulmonary infiltrates and six months later developed an advanced stage brain tumour (16).

Case reports with favourable outcomes

Giavina-Bianchi *et al.* and Caruso *et al.* reported cases of patients with EGPA in remission, who were given omalizumab

with significant improvement of asthma and no disease flares (17, 18).

Similarly, in a life-threatening form of EGPA treated by many immunosuppressants, omalizumab controlled a new relapse of asthma and the occurrence of nasal polyps also allowing to safely perform two additional courses of RTX, which previously evoked a severe bronchospasm requiring invasive mechanical ventilation (19).

Omalizumab was effective in two life-threatening cases of EGPA (20), and in a paediatric case of EGPA with extrapulmonary symptoms both resistant to many immunosuppressants (21).

Finally, in a further case omalizumab completely controlled asthma attacks, but the peripheral nerve complications and the basal FEV1 value were both unaffected (22) (Table I).

Case reports with adverse outcomes (failure of omalizumab in EGPA)

A 36-year-old woman affected by EGPA, after various attempts, was given omalizumab as a steroid sparing agent, unsuccessfully (23) (Table II).

Case reports with adverse outcomes (onset of EGPA under treatment with omalizumab)

In 2006 Winchester *et al.* first reported the case of a man affected by asthma who was given omalizumab and soon after developed EGPA (24). A severe form of EGPA with myocarditis and central nervous system involvement following the fourth injection of omalizumab was further described by Puechal *et al.* (25). Two years later, Bargagli described the case of a patient successfully treated with omalizumab who developed EGPA after steroid discontinuation (26).

In a comparable case, omalizumab could not control asthma symptoms and after 16 months the patient developed symmetric polyneuropathy receiving the diagnosis of EGPA (27).

In the case reported by Ruppert *et al.* omalizumab led to a marked improvement of asthma symptoms, but, after 4 months, EGPA developed (28).

Asthma and sinusitis symptoms significantly improved following omalizumab in the patient described by Cazzola *et*

Table I. Case reports assessing the role of omalizumab in EGPA (with favourable outcomes).

Author, Year, Ref	Subject	Baseline Disease features	Previous Therapy	Treatment	Results
Giavinia Bianchi <i>et al.</i> , 2007 (17)	1 EGPA Caucasian male 29 years old	Asthma, mononeuropathy, epididymo-orchitis, necrotizing vasculitis, eosinophilia, total IgE 398 IU/mL	EGPA remission apart from asthma, with high-dose inhaled corticosteroids, long-acting b2-agonists and several courses of steroid pulse therapy.	omalizumab 300 mg every 2 weeks for 3 months.	Improvement of FEV1 and eosinophilia.
Pabst <i>et al.</i> , 2008 (20)	1 EGPA Caucasian female 60 years old	Asthma, eosinophilia, skin eosinophilic vasculitis, nasal polyposis, total IgE 23 IU/mL	EGPA remission with oral prednisone (PDN). Four years later, on low dose therapy, onset of perimyocarditis (EF 30%), treated with PDN and cyclophosphamide (CYC). After development of proteinuria, CYC exchanged for AZA with no response.	omalizumab 150 mg every two weeks and then every four weeks.	Marked clinical improvement; AZA was stopped; maintenance therapy with PDN 2.5 mg/day, total IgE 93 IU/mL
	1 EGPA Caucasian female 65 years old	Bilateral vasculitic pulmonary infiltrates, eosinophilia, polyneuropathy, total IgE 930 IU/mL	EGPA remission with CYC and steroids. CYC replaced by AZA because of proteinuria. Worsening of clinical status and bronchial obstruction despite elevation of PDN to 70 mg/day.	omalizumab 150 mg every two weeks.	Radiological and clinical response with disappearing of dyspnea and eosinophils normalization, total IgE 157 IU/mL; new onset of diffuse interstitial infiltrates, progressive bronchial obstruction and eosinophilia two months after Omalizumab suspension, total IgE 248 IU/mL. Oral PDN increased to 70 mg/day and Omalizumab 150 mg every 2 weeks started again. The clinical status improved dramatically within 6 weeks, total IgE 235 IU/mL.
Iglesias <i>et al.</i> , 2014 (21)	1 EGPA Caucasian female 10 years old	Sinusitis, eosinophilia, asthma, pulmonary infiltrates, pericardial effusion, cutaneous vasculitis, total IgE 1,492 kU/l	Persistence of pulmonary infiltrates and onset of esophagi ulcers (daily vomiting) despite PDN, CYC and RTX.	omalizumab 300 mg every two weeks.	Resolution of eosinophilia, improving in respiratory and gastrointestinal symptoms at 8 weeks. PDN tapered to 5mg/day.
Graziani <i>et al.</i> , 2014 (22)	1 EGPA Caucasian female 56 years old	Mononeuritis multiplex, bilateral pulmonary infiltrates, asthma, eosinophilia, sinusitis.	Progressive clinical and radiological improvement with PDN 1 mg/kg. Recurrence of severe asthma attacks, requiring high doses of steroid therapy.	omalizumab 150 mg every two weeks.	Resolution of asthma and eosinophilia; significant persistent reduction of IgE levels; PDN reduced to 5 mg/day.
Aguirre Valencia <i>et al.</i> , 2017 (19)	1 EGPA Caucasian female 16 years old	Cutaneous and upper gastrointestinal tract vasculitis, asthma, eosinophilia, sinusitis.	Initial good response with PDN, plasmapheresis and CYC. Skin vasculitis flare with PDN 0.5 mg/kg/day, again treated with i.v. PDN and CYC. In the following months multiple flare-ups, eosinophilia, skin vasculitis, rhinitis and bronchospasms. After RTX onset, severe bronchospasms despite desensitization scheme. Ambulatory management with PDN, AZA and then MMF with good control of vasculitis but persistence of asthma and emergence of nasal polyps.	omalizumab 150 mg every two weeks.	Quick improvement in asthma and rhinitis followed by PDN withdrawal two months after Omalizumab initiation. Two additional cycles of RTX undertaken with no bronchospasm.
Caruso <i>et al.</i> , 2017 (18)	1 EGPA male 52 years old	Asthma, eosinophilia, paranasal sinus infiltrates with nasal polyps, pulmonary infiltrates with eosinophilic vasculitis, total IgE 647 kU/l	Despite high-dose inhaled steroids, montelukast, MTX and oral methylprednisolone (25 mg), the patient had occupational asthma (Anisakis simplex AS) with (FEV1/FVC) <70% and prebronchodilator FEV1 <80% of predicted; FEV1 78%, total IgE 647kU/L, specific IgE to AS 9.47 kU/L, AQLQ 2.88, ACT 8, Eosinophils 23%.	omalizumab 450 mg every two weeks.	Resolution of asthma and eosinophilia; FEV1 95%, total IgE 230 kU/L, Specific IgE to AS 2.8 kU/L, AQLQ 5.81, ACT 22, Eosinophils 7%.

Table II. Case report assessing the role of omalizumab in EGPA (with adverse outcomes).

Author, Year, Ref	Subject	Baseline disease features	Previous therapy	Treatment	Results
Lau <i>et al.</i> , 2011 (23)	1 EGPA female 36 years old	Eosinophilia, asthma, pulmonary infiltrates.	Despite a good clinical response, asthma symptoms relapsed when PDN was tapered to <20 mg/day. AZA caused severe hepatitis and MTX induced a worsening of blood eosinophilia.	omalizumab for 12 weeks	Severe disease exacerbation (hypereosinophilia and pulmonary infiltrates) when PDN was again tapered to <20 mg/ day.

al. Nevertheless, the patient soon developed a severe form of EGPA leading to acute respiratory failure requiring intravenous and oral steroids (29).

In a 45-year-old woman who was given omalizumab, EGPA appeared three months after oral steroid discontinuation (30) (Table III).

Retrospective cohort study

In 2009 Wechsler *et al.* tried to determine the number of cases of EGPA diagnosed in patients who had been treat-

Table III. Case reports reporting the onset of EGPA under treatment with omalizumab.

Author, Year	Subject	Baseline disease features	Previous therapy	Treatment	Results
Winchester <i>et al.</i> , 2006 (24)	1 Caucasian male 55 years old	History of asthma.	Not reported (NR)	omalizumab	EGPA onset (peripheral neuropathy, skin vasculitis, eosinophilia, asthma)
Puechal <i>et al.</i> , 2008 (25)	1 male 77 years old	25-year history of asthma with nasal polyposis. Two years before diagnosed with giant cell arteritis (GCA), total IgE 1449 IU/mL	GCA treated with oral steroids. Unsuccessful treatment with daily doses of inhaled corticosteroids, leukotriene modifiers, long-acting inhaled β_2 -agonist and oral corticosteroids.	omalizumab 375 mg every week.	After four injections development of severe form of EGPA (myocarditis and SNC involvement) successfully treated with steroids and CYC.
Bargagli <i>et al.</i> , 2008 (26)	1 male 47 years old	15-year-history of severe asthma.	PDN 8 mg/day.	omalizumab 375 mg every two weeks.	Oral steroids were progressively reduced; over four to six weeks the patient developed EGPA (pulmonary infiltrates, hyper eosinophilia, skin and bronchial vasculitis). Omalizumab was maintained. PDN and AZA achieved disease remission in three weeks.
Spina <i>et al.</i> , 2009 (27)	1 Caucasian male 42 years old	5-year-history of asthma, total IgE 580 IU/mL	One year after asthma onset of eosinophilia and eosinophilic pneumonia treated with PDN 1 mg/kg/day. Later, uncontrolled asthma.	omalizumab 375 mg every two weeks.	After 16 months, without oral steroid reduction, onset of symmetric polyneuropathy on 4 arms fulfilling diagnostic criteria for EGPA.
Ruppert <i>et al.</i> , 2008 (28)	1 Caucasian male 62 years old	4-year-history of allergic asthma, total IgE 158 IU/mL	Unsuccessful treatment with fluticasone (2000 mg/d), salmeterol (200 mg/d), and mean PDN 5 mg/day.	omalizumab 150 mg every four weeks.	Optimal asthma control and PDN discontinuation but in one year onset of severe EGPA (fever, weight loss, massive abdomen cervical and left cheek infiltrate, eosinophilia). Omalizumab was stopped and the patient was successfully treated with PDN and CYC.
Cazzola <i>et al.</i> , 2009 (29)	1 male 23 years old	2-year-history of asthma, maxillary sinusitis with polyps.	Unsuccessful treatment with fluticasone 250 lg + salmeterol 50 lg every 12 h, montelukast 10 mg/die, and salbutamol on demand.	omalizumab 300 mg every two weeks.	After third infusion worsening of asthma. After fourth infusion development of severe EGPA (pulmonary infiltrates with acute respiratory failure, eosinophilia, asthma, sinusitis). Total IgE >1000 IU/mL. Omalizumab suspended. Remission soon obtained with PDN.
Cisneros <i>et al.</i> , 2009 (30)	1 female 45 years old	Asthma, recurrent nasal polyps, pulmonary infiltrates, total IgE 600 UI/mL	Unsuccessful treatment with PDN 10 mg every two days.	omalizumab 450 mg every two weeks.	Asthma clinical and functional improvement with subsequent discontinuation of oral steroids. Three months later development of both legs skin vasculitis, confirming the initial suspicion of EGPA.

ed with omalizumab using the global safety database (Argus) maintained by Novartis covering the time period from June 2003 to June 2007. Following the database research 34 possible EGPA cases were identified, including 28 spontaneous reports and 6 reports from clinical trials. Among those, 13 were finally identified to be definitely or probably EGPA. In that period the reporting rate of EGPA in the United States was estimated to be 46 cases per million person-years. Taking into account the 13 definite/probable cases, the reporting rate was 149 cases per million person-years. When both definite/probable and possible reports of EGPA were considered, the reporting rate was estimated to be even 194 cases per million person-years. The average time between receiving omalizumab and the onset of EGPA was six months. Males were higher in number than females (9 vs. 4). The age was quite variable. All patients

presented asthma and eosinophilia. Four patients experienced neuropathy, two of whom received a diagnosis of mononeuritis multiplex. Pleural effusion was finally detected in at least six patients. In eight cases steroid was tapered just before the onset of EGPA symptoms and in the remaining cases an EGPA diagnosis was established, but insufficient information were provided for further assessment (31).

Noteworthy Jachiet *et al.* evaluated the efficacy and the safety of omalizumab in 17 patients with refractory and/or relapsing EGPA through a nationwide French retrospective multicentre study. At the time of the diagnosis of EGPA, all patients had asthma and blood eosinophilia, 16 patients (94%) had sinonasal abnormalities, 9 (53%) had pulmonary infiltrates, 6 (35%) had tissue eosinophilia infiltration biopsy specimen, 5 (29%) had peripheral neuropathy, and 4 (24%) had cardiac

involvement. The median number of treatment lines before omalizumab was three, including corticosteroids in all patients and immunosuppressive or immunomodulatory agents in 15 patients (88%). 12 months after omalizumab initiation prednisone dosage decreased significantly at each time point compared with the baseline value, whereas no significant difference was found for the eosinophil count, the Birmingham Vasculitis Activity Score (BVAS) and the FEV. Twenty-two months after omalizumab initiation, 6 patients (35%) achieved a complete response, 5 patients (30%) achieved a partial response, whereas 6 patients (35%) had refractory disease, among whom four patients presented disease relapsing: two developed severe asthma flares whereas the two others developed retrobulbar optic neuritis, unresponsive to high-doses of steroids and immunosuppressants. As expected, no severe

adverse events related to omalizumab injection were reported (32).

In 2018 Celebi Sozener *et al.* evaluated functional and clinical effectiveness of omalizumab in 18 patients during 5 years of treatment. The main manifestations were sinusitis (83.3%), pulmonary infiltrates (72%) and nasal polyposis (33.3%). At last evaluation 10 patients (55.6%) responded completely whereas 7 patients (38.9%) had no improvement. To all time points a significant reduction in mean OCD dose (from 15.7 mg/day to 4.9 mg/day at fifth year), asthma exacerbation and hospitalisation rates was achieved. A significant improvement of asthma control test (ACT) and FEV1% was observed only at sixteenth week and eosinophil count decreased with no statistical significance (33).

Prospective cohort study

Detoraki *et al.* evaluated in a 36-month follow-up observational study the role of omalizumab as maintenance therapy in EGPA. All five participants had previously received an immunosuppressive therapy (CYC or AZA) and/or glucocorticoids. At the time of the recruitment four patients were receiving moderate dosage of oral PDN (mean value 22.5 mg/day), whereas one patient was in clinical remission and three months before discontinued oral glucocorticoid therapy. Nevertheless, all of them were receiving therapy with inhaled long-acting b2 agonists and inhaled steroids at constant doses. After six months of treatment an improvement (although not statistically significant) in FEV1 was observed and constantly maintained throughout the 36 months of observation. Similarly, the asthma symptoms improved throughout the entire duration of the study. After 24 months of treatment, eosinophil count was significantly lower than at baseline. Interestingly, the dose of PDN significantly decreased from month 6 to the end of the study and was discontinued in two patients after 12 months of treatment. 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. Finally, no worsening

of respiratory, cutaneous, cardiologic or neurologic symptoms was documented (34).

Discussion

Overall, the available evidence suggests that omalizumab might be effective in EGPA, but also that it could play a role, not completely ascertained, in the development of EGPA in a very minority of asthmatic patients.

Omalizumab as a remedy for EGPA

As EGPA patients with atopy present more severe uncontrolled asthma manifestations but less severe vasculitis manifestations (35) the positive effects of omalizumab in EGPA patients could be related to an atopic status of the patients. In this regard, the available evidence, with only one variant case report (24), support the use of omalizumab as maintenance therapy of EGPA in patients with a total control of extrapulmonary, but not of the asthma symptoms (18-20, 31, 33).

The same conclusion does not apply to severe forms of EGPA, although two life-threatening cases of EGPA unresponsive to immunosuppressants eventually responded to omalizumab (21, 22). Indeed, in patients with refractory EGPA omalizumab could demonstrate a steroid sparing effect, but effects on disease activity and pulmonary function were mild and eosinophil count, already low at baseline, did not change (33, 34).

One of the possible explanations of the beneficial effect of omalizumab in EGPA could be the down-regulation of the high affinity receptor for IgE (FcεRI) expressed on mast cells. As eosinophil activation and consequent release and production of several pro-inflammatory mediators strongly depends from the interaction with mast cells, their reduction could therefore explain the parallel decrease on eosinophils number and activation observed with omalizumab (36).

Omalizumab as a risk factor for EGPA

Steroid reduction or suspension usually preceded EGPA onset during omalizumab therapy (27-29, 31) and in two

cases EGPA clinical remission was achieved despite omalizumab prosecution (27, 31). In only two cases (25,30) steroid tapering did not herald EGPA onset. Unique is the case of a patient previously affected by GCA, a large-vessel vasculitis, who developed EGPA one year after steroid withdrawal and after four courses of omalizumab (26). Finally, prednisone tapering was recognised to precede EGPA onset in the retrospective analysis performed by Wechsler *et al.* (31).

The current evidence seems to exclude that omalizumab is causally linked to the onset of EGPA. The most plausible hypothesis, concerning the majority of cases, is that omalizumab treatment, by allowing the reduction of corticosteroids, can unmask EGPA. Nevertheless, we cannot rule out that the pathogenic heterogeneity in EGPA might, in selected cases, result in a paradoxical response to omalizumab through the loss of counter-regulatory mechanisms. Indeed, interesting information is expected to derive from the expanding use of mepolizumab, an IL-5 inhibitor, in asthma and EGPA. In this context, mepolizumab achieved remission in a high proportion of EGPA patients (37), whereas no EGPA onset has been so far reported among treated eosinophilic asthmatic patients, despite significant associated steroids reduction (38). If these preliminary data will be confirmed by real life experience, they will strengthen the hypothesis of a pathogenic role occasionally exerted by the omalizumab in the onset of EGPA. The different cellular targets of mepolizumab, mainly the eosinophils (38), in comparison to omalizumab, with a wider variety of effects not limited to basophils and mast cells, but also including eosinophils and cytokine expression, might underlie the difference (39, 40). Indeed, due its pleiotropic effects, omalizumab might be able to perturb the anti-inflammatory status in selected patients and, thus, promote EGPA. In any case, steroids should be tapered very cautiously and the health status should be carefully monitored to timely detect a new onset EGPA after starting omalizumab therapy.

Limitations

The main limitation is related to the poor methodological quality of the included studies, mainly case reports. Indeed, selection bias towards unusual or favourable cases unavoidably affects conclusions largely based on case reports. However, it must be pointed out that EGPA is a very rare disease and organizing clinical trial is a challenge. In addition, despite the retrospective design of the included studies, in the context of rare diseases, the case reporting may detect novelties, generate hypotheses and strengthen pharmacovigilance.

Conclusion

In conclusion, omalizumab may be effective as corticosteroid-sparing agent in EGPA patients with severe asthmatic manifestations. In these patients the dosage of omalizumab should be calculated according to IgE levels and body weight. On the contrary, its use is debatable in severe forms of EGPA and in the absence of eosinophilia. If the objective of the treatment is to achieve clinical remission in patients with severe forms of EGPA the treatment should be more intensive (up to 600 mg every two weeks) while the duration and the interval of administration should be established in relation to individual clinical response in order to avoid exacerbations of the disease. The dosage of omalizumab used in EGPA patients was different according to different cases, underlying the absence of standardised fixed dosage in EGPA. It could also represent an advantage as the dosage could be modified in relation to the clinical response to the treatment.

Finally, an increased risk of EGPA onset in asthmatic patients treated with omalizumab seems plausible, but the profile of risk is unclear and the cautious tapering of corticosteroids is likely to prevent the majority, but not all these cases of EGPA, as if omalizumab might be occasionally involved in the pathogenesis. These recommendations represent the common sense implications of the limited available evidence and are worthy of confirmation by clinical trials and epidemiological studies. Meanwhile, the systematic and structured reporting of the effects of

omalizumab in EGPA to fill a dedicated register is highly desirable to overcome the limitations due to selective reporting and uneven collection of data.

References

1. NAVINES-FERRER A, SERRANO-CANDELAS E, MOLINA-MOLINA GJ, MARTIN M: IgE-related chronic diseases and anti-IgE-based treatments. *J Immunol Res* 2016; 2016: 8163803.
2. MENZELLA F, GALEONE C, FORMISANO D *et al.*: Real-life efficacy of omalizumab after 9 years of follow-up. *Allergy Asthma Immunol Res* 2017; 9: 368-372.
3. HANANIA NA, ALPAN O, HAMILOS DL *et al.*: Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011; 154: 573-82.
4. SUSSMAN G, HEBERT J, BARRON C *et al.*: Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol* 2014; 112: 170-4.
5. GOULD HJ, SUTTON BJ: IgE in allergy and asthma today. *Nat Rev Immunol* 2008; 8: 205-17.
6. BOBOLEA I, BARRANCO P, FIANDOR A, CABANAS R, QUIRCE S: Omalizumab: a potential new therapeutic approach for aspirin-exacerbated respiratory disease. *J Investig Allergol Clin Immunol* 2010; 20: 448-9.
7. KAYA H, GUMUS S, UCAR E *et al.*: Omalizumab as a steroid-sparing agent in chronic eosinophilic pneumonia. *Chest* 2012; 142: 513-6.
8. JACHET M, FLAGEUL B, DEROUX A *et al.*: The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. *Arthritis Rheumatol* 2015; 67: 527-34.
9. AURICH S, SIMON JC, TREUDLER R: Omalizumab does not improve skin lesions in a patient with hypocomplementemic urticarial vasculitis syndrome. *J Eur Acad Dermatol Venereol* 2017; 31: 395-7.
10. NUCERA E, BASTA F, BUONOMO A *et al.*: A case of hypocomplementemic urticarial vasculitis syndrome successfully treated with omalizumab. *J Investig Allergol Clin Immunol* 2017; 27: 382-4.
11. COMAROMOND C, PAGNOUX C, KHELLAF M *et al.*: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013; 65: 270-81.
12. VAGLIO A, STREHL JD, MANGER B *et al.*: IgG4 immune response in Churg-Strauss syndrome. *Ann Rheum Dis* 2012; 71: 390-3.
13. MONTI S, BOND M, FELICETTI M *et al.*: One year in review 2019: vasculitis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S3-19.
14. SAKU A, FURUTA S, HIRAGURI M *et al.*: Longterm outcomes of 188 Japanese patients with eosinophilic granulomatosis with polyangiitis. *J Rheumatol* 2018; 45: 1159-66.
15. GROH M, PAGNOUSX, BALDINI C *et al.*: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015; 26: 545-53.
16. BOREKCI S, AYDIN O, HATEMI G, GEMICIO-GLU B: Development of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) and brain tumor in a patient after more than 7 years of omalizumab use: A case report. *Int J Immunopathol Pharmacol* 2015; 28: 134-7.
17. GIAVINA-BIANCHI P, GIAVINA-BIANCHI M, AGONDI R, KALIL J: Three months' administration of anti-IgE to a patient with Churg-Strauss syndrome. *J Allergy Clin Immunol* 2007; 119: 1279.
18. CARUSO C, GENCARELLI G, GAETA F, VALLUZZI RL, RUMI G, ROMANO A: Efficacy of omalizumab treatment in a man with occupational asthma and eosinophilic granulomatosis with polyangiitis. *Ann Allergy Asthma Immunol* 2018; 120: 209-11.
19. AGUIRRE-VALENCIA D, POSSO-OSORIO I, BRAVO JC, BONILLA-ABADIA F, TOBON GJ, CANAS CA: Sequential rituximab and omalizumab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Clin Rheumatol* 2017; 36: 2159-62.
20. PABST S, TIYERILI V, GROHE C: Apparent response to anti-IgE therapy in two patients with refractory "forme fruste" of Churg-Strauss syndrome. *Thorax* 2008; 63: 747-8.
21. IGLESIAS E, CAMACHI LOVILLO M, DELGADO PECCELLIN I *et al.*: Successful management of Churg-Strauss syndrome using omalizumab as adjuvant immunomodulatory therapy: first documented pediatric case. *Pediatr Pulmonol* 2014; 49: 78-81.
22. GRAZIANI A, QUERCIA O, GIRELLI F, MARTELLI A, MIRICI CAPPA F, STEFANINI GF: Omalizumab treatment in patient with severe asthma and eosinophilic granulomatosis with polyangiitis. A case report. *Eur Ann Allergy Clin Immunol* 2014; 46: 226-8.
23. LAU EM, COOPER W, BYE PT, YAN K: Difficult asthma and Churg-Strauss-like syndrome: a cautionary tale. *Respirology* 2011; 16: 180-1.
24. WINCHESTER DE, JACOB A, MURPHY T: Omalizumab for asthma. *N Engl J Med* 2006; 355: 1281-2.
25. PUECHAL X, RIVERAU P, VINCHON F: Churg-Strauss syndrome associated with omalizumab. *Eur J Intern Med* 2008; 19: 364-6.
26. BARGAGLI E, MADIONI C, OLIVIERI C, PENZA F, ROTTOLI P: Churg-Strauss vasculitis in a patient treated with omalizumab. *J Asthma* 2008; 45: 115-6.
27. SPINA MF, MIADONNA A: Role of omalizumab and steroids in Churg-Strauss syndrome. *J Allergy Clin Immunol* 2009; 124: 600-1.
28. RUPPERT AM, AVEROUS G, STANCIU D *et al.*: Development of Churg-Strauss syndrome with controlled asthma during omalizumab treatment. *J Allergy Clin Immunol* 2008; 121: 253-4.
29. CAZZOLA M, MURA M, SEGRETI A, MATTEI MA, ROGLIANI P: Eosinophilic pneumonia in an asthmatic patient treated with omalizumab therapy: forme-fruste of Churg-Strauss syndrome? *Allergy* 2009; 64: 1389-90.

30. CISNEROS C, SEGRELLES G, HERRAEZ L, GONZALEZ A, GIRON R: Churg-Strauss syndrome in a patient treated with omalizumab. *J Investig Allergol Clin Immunol* 2013; 23: 515-6
31. WECHSLER ME, WONG DA, MILLER MK, LAWRENCE-MIYASAKI L: Churg-Strauss syndrome in patients treated with omalizumab. *Chest* 2009; 136: 507-18.
32. JACHET M, SAMSON M, COTTIN V *et al.*: Anti-IgE monoclonal antibody (Omalizumab) in refractory and relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss): data on seventeen patients. *Arthritis Rheumatol* 2016; 68: 2274-82.
33. CELEBI SOZENER Z, GORGULU B, MUNGAN D *et al.*: Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): single-center experience in 18 cases. *World Allergy Organ J* 2018; 11: 39
34. DETORAKI A, DI CAPUA L, VARRICCHI G, GENOVESE A, MARONE G, SPADARO G: Omalizumab in patients with eosinophilic granulomatosis with polyangiitis: a 36-month follow-up study. *J Asthma* 2016; 53: 201-6.
35. BERTI A, VOLCHECK GW, CORNEC D, SMYTH RJ, SPECKS U, KEOGH KA: Severe uncontrolled asthma and overall survival in atopic patients with eosinophilic granulomatosis with polyangiitis. *Respir Med* 2018; 142: 66-72.
36. GANGWAR RS, FRIEDMAN S, SEAF M, LEVISHAFFER F: Mast cells and eosinophils in allergy: Close friends or just neighbors. *Eur J Pharmacol* 2016; 778: 77-83.
37. WECHSLER ME, AKUTHOTA P, JAYNE D *et al.*: Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017; 376: 1921-32.
38. PELAIA C, VATRELLA A, BUSCETI MT *et al.*: Severe eosinophilic asthma: from the pathogenic role of interleukin-5 to the therapeutic action of mepolizumab. *Drug Des Devel Ther* 2017; 11: 3137-44.
39. ASSAYAG M, MOSHEL S, KOHAN M, BERKMAN N: The effect of omalizumab treatment on the low affinity immunoglobulin E receptor (CD23/fc epsilon RII) in patients with severe allergic asthma. *Allergy Asthma Proc* 2018; 39: 36-42.
40. YALCIN AD, CILLIA, BISGIN A, STRAUSS LG, HERTH F: Omalizumab is effective in treating severe asthma in patients with severe cardiovascular complications and its effects on sCD200, d-dimer, CXCL8, 25-hydroxyvitamin D and IL-1 β levels. *Expert Opin Biol Ther* 2013; 13: 1335-41.