Exploration of Asthma & Allergy

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Open Access Review

New therapeutic approaches with biological drugs for eosinophilic granulomatosis with polyangiitis

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Academic Editor: Karl-Christian Bergmann, Charité – Universitätsmedizin Berlin, Germany

Received: December 12, 2022 **Accepted:** April 12, 2023 **Published:** June 8, 2023

Cite this article: Carrón-Herrero A, Pelaia C, Paoletti G. New therapeutic approaches with biological drugs for eosinophilic granulomatosis with polyangiitis. Explor Asthma Allergy. 2023;1:31–48. https://doi.org/10.37349/eaa.2023.00006

Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a multiorganic syndrome that affects the cardiovascular, neurologic, renal, and gastrointestinal systems with an incidence ranging from 0 case to 67 cases per one million person-years, and its pathophysiology remains unknown. It is believed that genetic factors, the environment, and changes in immune system function contribute to the development of EGPA, overlapping the immune mechanisms of vasculitides and the pathologic mechanisms in eosinophilic syndromes. This disease is commonly divided into two phenotypes depending on the presence of antineutrophil cytoplasmic antibodies (ANCA). ANCA-positive patients usually have more vasculitic manifestations like peripheral neuropathy, purpura, renal involvement, and biopsy-proven vasculitis. The keystone of EGPA therapy is systemic corticosteroids (CS) as monotherapy or in combination with other immunosuppressive treatments, and recently the efficacy of eosinophil-targeted biotherapy, anti-interleukin-5 (IL-5), has been shown to be efficacious in EGPA. Although this phenotype/phase distinction has not yet had an impact on the current treatment strategies, emerging targeted biotherapies under evaluation could lead to a phenotype-based approach and personalised treatment regimens for EGPA patients. The present review describes the new therapeutical approaches with biological drugs for EGPA.

Keywords

Eosinophilic granulomatosis with polyangiitis, biological therapies, c-antineutrophil cytoplasmic antibodies, mepolizumab, benralizumab, reslizumab, omalizumab, rituximab

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is one of the antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides [1]. In accordance with the latest International Chapel Hill Consensus, it is an eosinophilic and necrotizing granulomatous vasculitis affecting small to medium vessels, the respiratory tract, where bronchial asthma and chronic rhinosinusitis are the main characters [1, 2]. It is a multiorganic syndrome with a wide range of manifestations, affecting the skin, neurologic, cardiovascular, renal, and gastrointestinal systems [1, 2]. It is a very rare disease with an incidence ranging from 0 case to 67 cases per one million person-years [3].

Over 30 years ago, the American College of Rheumatology (ACR) published classification criteria for EGPA. However, these criteria have never been validated due to the small number of patients included, which were developed using data from only 20 patients [4]. It is not until 2022 that the ACR/European Alliance of Associations for Rheumatology (EULAR) endorses and publishes the new classification criteria for EGPA [5]. However, it is necessary to know that the Birmingham vasculitis activity score (BVAS) is a validated tool with different items that allows the identification of disease activity in patients diagnosed with EGPA [6].

To understand how EGPA affects patients, this disease is often classified into two phenotypes based on the presence of ANCA targeting myeloperoxidase (MPO) status [7–9]. MPO-ANCA are present in about 31% and 38% of patients and are associated with the vasculitis pattern of the disease. In juxtaposition, patients without MPO-ANCA are at risk of cardiac involvement, being the main cause of morbidity and mortality [7–9]. ANCA-positive patients are more likely to have features of vasculitis with peripheral neuropathy, purpura, renal involvement, and biopsy-proven vasculitis [9]. It is important to emphasize that 3 phases characterize EGPA (Figure 1) that can overlap and progress at varying intervals: the prodromal period, where asthma and other allergic manifestations are the main features; the eosinophilic phase with blood and tissue eosinophilia; and the vasculitis phase with small vessel necrotising vasculitis [1, 10].

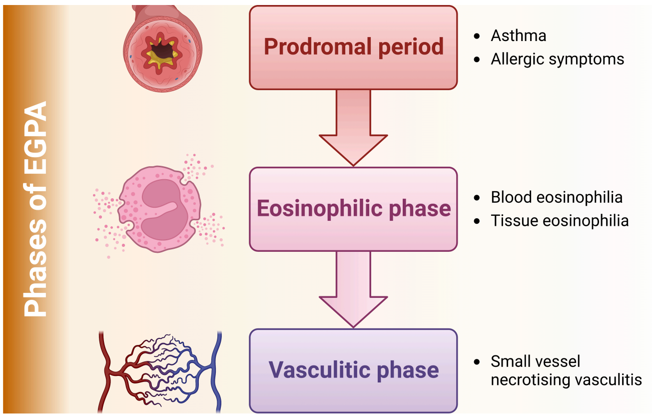

Figure 1. Phases of EGPA

Although this phenotype/phase distinction has not yet had an impact on the current treatment strategy, emerging targeted biotherapies under evaluation could lead to a phenotype-based approach and personalised treatment regimens for EGPA patients [9].

The present review describes the new therapeutical approaches with biological drugs for EGPA.

Pathogenesis

The pathogenesis of EGPA is still an unknown subject. Several factors are thought to contribute to its pathophysiology. Genetic predisposition and epigenetic changes are factors that dysregulate the proper functioning of the immune system and contribute to the development of EGPA (Figure 2) [7]. There has even been a recent case report of a patient who developed EGPA after the RNA-coronavirus disease (COVID) vaccine [11]. It is considered by many authors to be an overlap between the immune mechanisms of vasculitides and the pathological mechanisms in eosinophilic syndromes [7, 10].

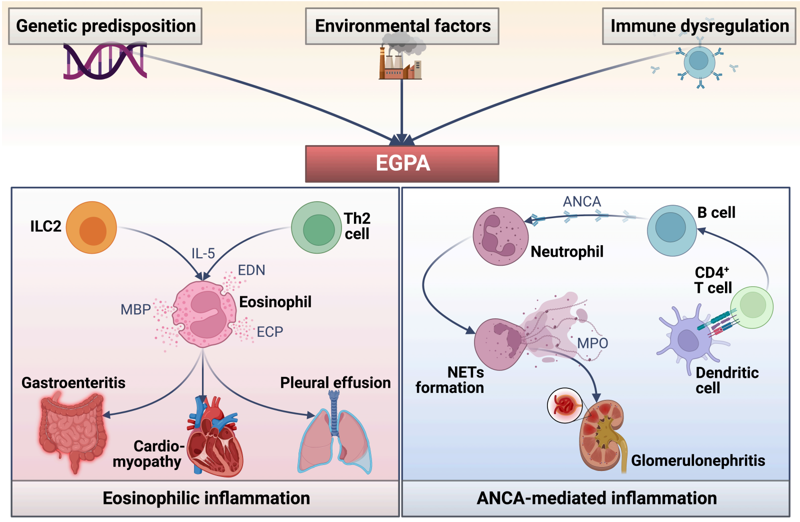

Figure 2. Pathophysiology of EGPA. ICL2: intracellular loop 2; IL-5: interleukin-5; EDN: eosinophil-derived neurotoxin; Th2: T helper 2; MBP: major basic protein; ECP: eosinophil cationic protein; NETs: neutrophil extracellular traps

Eosinophils are thought to play a significant role in the pathogenesis of EGPA [1, 10, 12] because they participate in all three stages of the disease [1, 10]. Eosinophils release their granules containing stored cytotoxic proteins and toxins such as EDN, MBP, eosinophil peroxidase, and ECP, leading to tissue damage [12]. The increase in blood and tissue eosinophils is widely thought to be the result of Th2 cytokine production by $CD4^+$ T cells, particularly IL-5, the most potent stimulator of eosinophil proliferation and functional activation [13–15].

IL-5 is increased in patients with EGPA in active disease and can promote the adhesion of eosinophils to vascular endothelium. Thus, the elevated production of IL-5 may be relevant pathogenetically, not only for eosinophilia but also for the development of vasculitis by promoting transvascular migration and functional activation of eosinophils [14–17]. Most of the biological therapies being studied are aimed at blocking this IL. Despite the complex pathophysiological mechanisms associated with EGPA, much progress has been made in understanding the mechanisms underlying EGPA; however, further studies are needed to clarify its pathophysiology.

Classification criteria for EGPA

Recently in February 2022, the ACR and EULAR published the new validated classification criteria for EGPA [5]. This classification should be applied to categorize a patient as having EGPA when a diagnosis of small or medium-vessel vasculitis has been suspected. These criteria are divided into clinical criteria and laboratory and biopsy criteria. A score ≥ 6 is needed for the classification of EGPA [5], as can be seen below:

(A) Clinical criteria:

a. Obstructive airway disease (+ 3)

b. Nasal polyps (+ 3)

c. Mononeuritis multiplex (+ 1)

(B) Laboratory and biopsy criteria:

a. Blood eosinophil count ≥ 1 × 10^9/L (+ 5)

b. Extravascular eosinophilic-predominant inflammation on biopsy (+ 2)

c. Positive test for cytoplasmatic ANCA (cANCA) or antiproteinase 3 (anti-PR3) antibodies (– 3)

d. Hematuria (– 3)

The keystone of EGPA therapy is systemic corticosteroids (CS) used as monotherapy or in combination with other immunosuppressive agents (ISAs) [1, 9, 12]. The therapeutic choice is guided by the type and severity of organ involvement and scoring systems, defined by the Five Factor Score (FFS) [18]. An FFS of 0 signifies non-severe disease without organ involvement, and an FFS of ≥ 1 depicts severe disease with organ involvement. Therefore, if FFS is 0, systemic glucocorticoids are used as monotherapy. If FFS ≥ 1 or life-threatening or organ-threatening symptoms, ISAs including azathioprine, cyclophosphamide, methotrexate, mofetil mycophenolate, or rituximab (RTX) are added to the CS [9, 12].

CS has been associated with notably improved remission rates and reduced disease mortality [18]. However, to date, no controlled trials have ever been made, and it is inevitable that CS changed EGPA prognosis [9].

ISAs, as previously mentioned, are commonly prescribed in combination with CS to treat severe EGPA [1, 9, 12]. Cyclophosphamide is the most ISAs defined to control severe vasculitis manifestations and is the first choice for cardiac involvement [1, 18–20].

Methotrexate and azathioprine are given, after cyclophosphamide induction, as maintenance therapy or when cyclophosphamide is contraindicated [8, 18]. After remission, the most used in the maintenance phase are methotrexate, azathioprine, or mofetil mycophenolate [1, 21–23].

For refractory disease, relapses, problems associated with CS dependence, and asthma symptoms that often persist after the vasculitis is in remission, effective agents that have successfully treated other eosinophil-related disorders are currently being developed, creating new therapeutic possibilities for patients with EGPA [9]. Continuing advances in research and the development of new biological therapies have demonstrated the efficacy of an eosinophil-targeted biotherapy, anti-IL-5 to be effective in EGPA [9, 12, 24]. However, further studies are needed to determine which patients with EGPA would benefit from these targeted therapies.

New targeted therapies

Mepolizumab

Mepolizumab is a humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) against free IL-5 that selectively inhibits eosinophilic inflammation [12, 25, 26]. Mepolizumab prevents IL-5 from binding to the α-subunit receptor, predominantly expressed in human eosinophils [7, 12, 27]. Due to its characteristics, mepolizumab has been investigated to treat eosinophils-related disorders such as atopic dermatitis, chronic rhinosinusitis, hypereosinophilic syndrome, and severe eosinophilic asthma and EGPA has recently been included in the therapeutic range. In 2015, mepolizumab was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an add-on therapy in severe eosinophilic asthma at a dose of 100 mg every four weeks [12, 24, 28, 29], resulting in a reduction in asthma exacerbations and the need for systemic CS treatment [26].

In 2010 was published the first case report of the successful use of mepolizumab was in a patient with refractory ANCA-negative EGPA. The patient presented hypereosinophilia and interstitial pneumonia with 60% eosinophils in bronchoalveolar lavage fluid and myocarditis. They started 750 mg of intravenous (IV) mepolizumab every four weeks, achieving normalization of blood eosinophils counts and asthma control after the first dose. However, the asthma control test (ACT) or lung function was not reported in this study. Complete normalization of chest tomography was developed after the second infusion, persisting after 6 months [30].

Subsequently, a small open-label pilot study treated 7 CS-dependent EGPA patients with 750 mg IV mepolizumab every 4 weeks for 4 months. They demonstrated that mepolizumab allowed substantial CS tapering while maintaining clinical stability. However, on mepolizumab cessation, the EGPA manifestation recurred, necessitating CS bursts with a more gradual resurgence of the blood eosinophil percentage [31].

A follow-up study of 10 patients with refractory EGPA treated with 9 infusions of 750 mg IV mepolizumab and then switched to methotrexate to achieve remission was subsequently published [32]. CS was at as low a dose as possible to the physician's criteria, no CS withdrawal protocol was discussed. The mean follow-up was 22 months, with 3/10 patients still in remission after 143 weeks of stopping mepolizumab. However, 66.6% had to increase the CS intake, and the eosinophils counts rose after discontinuation of mepolizumab infusions [32]. This study demonstrated that mepolizumab could induce temporary remission in EGPA in a small population.

The studies above were pivotal to progress in treating EGPA and pointed out a potential benefit of mepolizumab. However, it was not until 2017 that the EGPA mepolizumab study team published the results of the mepolizumab or placebo for EGPA or mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis study (MIRRA) [24], a multicenter, double-blind, parallel-group, phase III trial of 136 patients with relapsing or refractory EGPA receiving systemic CS, 68 participants were assigned to receive 300 mg subcutaneous (SC) plus standard care every 4 weeks for 52 weeks, and 68 patients were in the placebo group. Organ or life-threatening EGPA was excluded. The MIRRA trial defined remission as a reduction in the CS dose according to its standardized program and a zero score from BVAS and prednisone ≤ 4 mg/day. Mepolizumab led to significantly more accrued weeks (≥ 24 weeks) of remission than placebo (28% *vs.* 3%); a higher percentage of participants in remission at both week 36 and week 48 (32% *vs.* 3%), and the rate of reduction of prednisone or equivalent to 4 mg/day or less per day was 44% in mepolizumab and 7% in placebo. The time to first relapse over a 52-week period was significantly longer in participants who received mepolizumab than those who received a placebo (56% *vs.* 82%), and vasculitis relapses occurred in 43% in the mepolizumab group *vs.* 67% receiving placebo.

The MIRRA trial led to the 2017 FDA authorization of 300 mg SC mepolizumab every 4 weeks as the first drug to be approved explicitly for EGPA [24, 28].

A posthoc analysis [33] investigated the clinical benefit of mepolizumab, defined as a 50% or more significant reduction in oral CS dose during weeks 48 to 52 or no EGPA relapses. Patients in the mepolizumab group reduced the oral CS intake definition (78% *vs.* 32%), and 87% of patients experience no EGPA relapses *vs.* 53% in the placebo group [33].

After the FDA approved mepolizumab for EGPA at a monthly dose of 300 mg, a recent real-life observational study of 16 patients suggested that mepolizumab at a dose of 100 mg 4 weeks may have a role as a steroid/immunosuppressive sparing agent in patients affected by EGPA. They concluded that, despite the 100 mg dose, the proportion of patients who could discontinue oral CS was higher than in the MIRRA trial [34]. Another study reported the effectiveness of low-dose mepolizumab in 25 patients diagnosed with EGPA. A dose of 100 mg of mepolizumab was administered every 4 weeks, decreasing significantly daily CS dose with an improvement in ACT and quality of life scores. A significant reduction in asthma exacerbations and blood eosinophil was also observed. This study concluded that there was no significant difference between the dosages in terms of complete response [35].

A recent European multicenter observational study assessed mepolizumab's effectiveness and safety of 100 mg every 4 weeks and 300 mg every 4 weeks in a cohort of 203 patients with EGPA [36]. They suggested that mepolizumab 100 mg monthly might be an acceptable and valid alternative to the 300 mg dose with a lower rate of adverse events [36]. However, caution should be exercised when interpreting these data, as some reports suggest a risk of systemic disease flare in patients receiving mepolizumab at the dose for asthma control. Further randomised clinical trials with representative sample sizes and close long-term follow-ups are needed to compare the efficacy and safety of these two EGPA treatment regimens [36]. While all these studies assess the benefit of mepolizumab treatment in the EGPA, further studies are needed to determine its long-term efficacy.

Several clinical trials with mepolizumab are currently underway: E-merge (NCT05030155) [37], mepolizumab long-term study to asses real world safety and effectiveness of eosinophilic granulomatosis with polyangiitis (MARS, NCT04551989) [38], MEA115921 (NCT03298061) [39], EGPA Long-Term (NCT03557060) [40]. A summary of all relevant studies with mepolizumab can be found in Table 1.

Table 1. Mepolizumab therapy in patients with EGPA

Reference	Study design	Number of patients	Dose and route of administration	Results
Kahn et al. [30], 2010	Case report	1	750 mg IV monthly	Blood eosinophil normalization Clinical remission Chest tomography normalization Exacerbation reduction
Kim et al. [31], 2010	Open-label pilot study	7	750 mg IV monthly	CS reduction Reduce eosinophil counts Clinical stability Exacerbation reduction Lack of improvement in pulmonary function
Hermann et al. [32], 2012	Case report	10	750 mg IV monthly	9 Patients achieve clinical remission Decrease eosinophil count Exacerbation reduction Potential use to maintain remission in EGPA CS reduction
Wechsler et al. [24], 2017	Multicenter, double-blind, parallel-group, phase III trial	136	300 mg SC monthly	Significantly weeks (≥ 24 weeks) of remission than placebo (28% *vs.* 3%) The reduction of prednisone was 44% in mepolizumab and 7% in the placebo FDA authorization of 300 mg SC mepolizumab every 4 weeks as the first drug to be approved explicitly for EGPA
Steinfeld et al. [33], 2019	Analysis posthoc	-	300 mg SC monthly	Patients in the mepolizumab group reduce CS intake (78% *vs.* 32%) 87% Of patients experience no EGPA relapses *vs.* 53% in the placebo group
Carminati et al. [34], 2021	Real-life observational study	16	100 mg SC monthly	CS reduction ACT score improvement Exacerbation reduction No statistically significant differences in blood eosinophil reduction and pulmonary function
Özdel Öztürk et al. [35], 2022	Single-center retrospective real-life study	25	100 mg SC monthly	CS reduction ACT score, SNOT-22, and quality of life improvement. Exacerbation reduction Reduce eosinophils counts Improve lung function
Bettiol et al. [36], 2022	Multicenter observational study	203	100 mg SC monthly *vs.*300 mg monthly	Reduction in BVAS score CS reduction Reduce eosinophil counts No significant differences between 100 mg and 300 mg dose

SNOT: sinonasal outcome test; -: blank cell

Benralizumab

Benralizumab is a mAb that binds the IL-5 receptor, thus neutralizing eosinophils via antibody-dependent cellular cytotoxicity [41]. The clinical efficacy of benralizumab was investigated in two independent phase III trials [efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonist (SIROCCO) and benralizumab, an anti-IL-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA)] [41, 42]. Benralizumab significantly reduced the annual exacerbation rate, improved pulmonary function, and had a glucocorticoid-sparing effect in patients with eosinophilic asthma [40–42]. Benralizumab was approved for severe asthma in 2017 in the United States, and in 2018 in European countries [41–43].

In 2019, the first case report of a 59-year-old patient with MPO-ANCA-positive relapsing EGPA with purpura, mononeuritis, and high blood eosinophilia (17,640 eosinophils) who was treated with benralizumab SC at a 30 mg was published. After three weeks after the first administration, the patient achieved blood eosinophil count normalization, improvement of respiratory symptoms, decreased oral CS intake, and MPO-ANCA antibodies negativity. They concluded that reducing the MPO-ANCA levels might be helpful in controlling EGPA disease activity [44].

Subsequently, several case reports of EGPA patients treated with at least three 30 mg doses of benralizumab have been published in recent years [45–54], and all showed a reduction in oral CS intake and clinical remission [45–55]. These results should be taken with caution because these are single-patient case reports.

However, in 2020, Padoan et al. [56] described the clinical features in a series of 5 patients with refractory, CS-dependent asthma with EGPA, treated with a 30 mg dose of benralizumab SC every 8 weeks after the initial 3 doses administered every 4 weeks. All patients had a long-standing disease with a median duration of 20 months, 20% had an MPO-ANCA positivity rate, and none had cutaneous or cardiac involvement. At baseline, the median eosinophil count was 1,200 µL, with a BVAS of 4 and all patients received an oral CS dose above 10 mg, and 2/5 patients received ISAs as standard care. After 24 weeks of benralizumab, a significant reduction in CS intake was observed. Notably, 3 of 5 patients were able to withdraw CS completely. Alongside this, a complete depletion in circulating eosinophils was observed in all patients [56]. Although patients reported better disease control with an improvement in the ACT and quality of life, there was no statistically significant difference in lung function and a lack of improvement in ANCA-status [56]. Subsequently, Nanzer et al. [57] achieved similar results in a series of 11 patients with refractory EGPA who underwent a 24-weeks benralizumab treatment. The study successfully reduced CS intake, reduced total eosinophil count and BVAS scale, and improved ACT and quality of life. However, no improvements in lung function were reported [57].

Finally, a prospective 40-week open-label pilot study of benralizumab 30 mg administered SC in 10 patients with EGPA was conducted [58]. This study showed that benralizumab was well tolerated, reduced the median prednisone dose from 15 mg at baseline to 2 mg at the end of the treatment and 50% of the patients could completely withdraw CS. A significant decrease in absolute blood eosinophils was observed one month after benralizumab treatment compared to baseline. However, there were no significant differences in lung function, BVAS score, and quality of life questionnaire after benralizumab treatment [58]. Overall, this pilot study suggests that benralizumab safely reduces systemic CS dose and EGPA exacerbations in subjects with refractory and CS-dependent EGPA.

The use of benralizumab has significantly reduced total peripheral blood eosinophil counts and, in some cases, MPO-ANCA negativity [44], biomarkers that may predict disease prognosis. However, these benefits need to be evaluated in further randomized clinical trials.

Several clinical trials with Benralizumab are currently underway: benralizumab in the treatment of eosinophilic granulomatosis with polyangiitis (BITE, NCT03010436) [59], and efficacy and safety of benralizumab in EGPA compared to mepolizumab (MANDARA, NCT04157348) [60]. A summary of all relevant studies with benralizumab can be found in Table 2.

Table 2. Benralizumab therapy in patients with EGPA

Reference	Study design	Number of patients	Dose and route of administration	Results
Takenaka et al. [44], 2019	Case report	1	30 mg SC	Blood eosinophil normalization Clinical remission CS reduction MPO-ANCA negativation

Table 2. Benralizumab therapy in patients with EGPA (*continued*)

Reference	Study design	Number of patients	Dose and route of administration	Results
Padoan et al. [56], 2020	Case series	5	Initial 3 doses: 30 mg SC every 4 weeks Maintenance dose: 30 mg SC every 8 weeks	3 Patients completely withdraw from CS Complete depletion in blood eosinophils ACT improvement No statistically significant difference in lung function Lack of improvement in ANCA-status
Nanzer et al. [57], 2020	Case series	11	Initial 3 doses: 30 mg SC every 4 weeks Maintenance dose: 30 mg SC every 8 weeks	CS reduction Complete depletion in blood eosinophils BVAS improvement No statistically significant difference in lung function ACT improvement Quality of life improvement
Guntur et al. [58], 2021	Prospective open-label pilot study	10	Initial 3 doses: 30 mg SC every 4 weeks Maintenance dose: 30 mg SC every 8 weeks	Benralizumab was well tolerated 50% Of the patients could completely withdraw from CS Significant decrease in absolute blood eosinophils No significant differences in lung function, BVAS, and quality of life

Reslizumab

Reslizumab is an IgG4k humanized, mAb against IL-5 with a high IL-5-binding affinity, reducing eosinophil proliferation and airway inflammation approved for the treatment of severe eosinophilic asthma [12, 61].

A cohort of 9 patients [62] with oral CS-dependent EGPA and severe eosinophilic asthma were treated with reslizumab (3 mg/kg every four weeks). After 48 weeks of treatment, all patients achieved ≥ 50% maintenance oral CS reduction; even two patients could completely stop CS intake. This study observed that the oral CS reduction did not increase the peripheral eosinophil count. No significant changes were observed in pulmonary function and the BVAS [62].

Subsequently, an open-label pilot study evaluated the safety and efficacy of IV reslizumab (3 mg/kg every four weeks) in 10 subjects with MPO-ANCA negative EGPA. After 24 weeks of treatment, reslizumab was safe and well tolerated, and a reduction in oral CS intake was achieved in most of the participants [63]. The results from this study are similar to findings from other anti-IL-5 agents.

These studies suggest that reslizumab is a therapeutic option in EGPA patients with concomitant severe eosinophilic asthma and could help to reduce the use of CS [62, 63]. However, no significant improvement in overall BVAS scores was seen, suggesting that reslizumab may be less effective in controlling extrapulmonary manifestations in EGPA [62], but further studies are needed.

A summary of all relevant studies with reslizumab can be found in Table 3.

Table 3. Reslizumab therapy in patients with EGPA

Reference	Study design	Number of patients	Dose and route of administration	Results
Kent et al. [62], 2020	Case series	9	3 mg IV/kg every 4 weeks	CS reduction 2 Patients completely withdraw from CS No significant changes were observed in BVAS and lung function
Manka et al. [63], 2021	Prospective open-label pilot study	10	3 mg IV/kg every 4 weeks	Reslizumab was safe and well tolerated CS reduction No significant change in the asthma quality of life questionnaire Decrease in blood eosinophil count Improvement in BVAS

Omalizumab

Omalizumab is a recombinant humanized anti-IgE mAb which binds selectively to the Cε3 domain of the crystallizable fragment (Fc) fragment of the heavy chain of free IgE, thus preventing its interaction with the IgE receptors found on the surface of mast cells, basophils, eosinophils, and B cells, preventing its degranulation thus reducing the inflammatory activation cells and pro-inflammatory factors [64, 65].

Several studies with omalizumab have been published over the years with promising and beneficial results in the treatment of eosinophilic allergic asthma and it is therefore believed that it may also be considered an effective therapy in the treatment of patients with EGPA, particularly in those patients with uncontrolled asthma symptoms. Unfortunately, experience with omalizumab in the treatment of EGPA is limited to single case reports [66–70] or case series only [12]. Most of these cases describe an improvement in asthma symptoms, nasal polyposis, and reduction in blood eosinophil counts [66, 67, 69, 70].

In 2016, Jachiet et al. [71] reported a nationwide retrospective study of 17 patients with relapsing and/or refractory EGPA treated with at least one dose of omalizumab. They suggested that in EGPA patients with asthmatic and/or sinonasal manifestations, omalizumab may have an uncertain CS-sparing effect in these patients [71]. However, the high risk of severe EGPA flares, possibly due to the reduction in the CS dose, questioned the use of omalizumab for treating EGPA [71].

Subsequently, another single center reported its experience of 18 patients with EGPA treated with omalizumab. They concluded that omalizumab worked as a CS-sparing agent in all patients. and reduced asthma exacerbations. However, no decrease in the eosinophil count during treatment was observed [72]. Some of the studies mentioned above can be found in Table 4.

Table 4. Omalizumab therapy in patients with EGPA

Reference	Study design	Number of patients	Dose and route of administration	Results
Giavina-Bianchi et al. [66], 2007	Case report	1	300 mg SC every 2 weeks	Improvement of asthma Blood eosinophil reduction
Pabst et al. [67], 2008	Case report	2	Doses adjusted to weight and IgE levels	Blood eosinophil count normalization Immunosuppressive treatment was stopped
Lau et al. [68], 2011	Case report	1	Doses adjusted to weight and IgE levels	Exacerbation when CS was tapered No clinical or radiological improvement
Jachiet et al. [71], 2016	Retrospective multicentre study	17	Doses adjusted to weight and IgE levels	Mild efficacy for treating asthma, ear, nose, and throat (ENT) symptoms CS reduction BVAS improvement Blood eosinophil count did not decrease EGPA flares, possibly due to the reduction in the CS dose
Caruso et al. [70], 2018	Case report	1	450 mg SC every 2 weeks	Lung function improvement ACT and quality of life questionnaire improvement Blood eosinophil counts reduction CS reduction
Celebi Sozener et al. [72], 2018	Retrospective chart review	18	Doses adjusted to weight and IgE levels	10 Patients responded completely CS reduction Exacerbation reduction forced expiratory volume in the first second (FEV1) improvement No decrease in blood eosinophil count

Paradoxically some case reports describe an association between the use of omalizumab and the onset of EGPA after withdrawal of oral CS [73–77]. These findings may hinder the use of omalizumab for the treatment of EGPA [71].

Omalizumab may be effective as a CS-sparing agent in EGPA with severe allergic asthma. Still, there is little evidence of improvement in extrapulmonary manifestations [65], but many more high-quality studies are needed.

RTX

RTX is an anti-CD20 chimeric mouse-human mAb. It induces B-cell depletion in peripheral blood [9, 78, 79]. Currently, it is licensed in Europe for rheumatoid arthritis and in severe ANCA-associated vasculitis (AAV) [78] with an acceptable safety profile and is currently approved by the EMA and FDA as drug remission induction therapy in these patients [79–82]. However, in the pivotal trials with RTX performed in patients with AAV [80–82], patients with EGPA were excluded because this vasculitis is less frequent than other AAV [79].

The evidence of RTX benefits in patients with EGPA is limited to case series and small-sized [83–88], open-label studies on refractory/relapsing EGPA [9, 89].

In 2011, a prospective single-center, open-label pilot study with 3 patients using RTX (375 mg/m^2 every 4 weeks) for induction of remission in refractory/relapsing EGPA patients with renal involvement was conducted. All patients were ANCA-positive and were followed up for 1 year and all of them achieved renal remission within the first 3 months [89].

A single-center cohort of 9 patients with refractory or relapsing EGPA treated with RTX was published [85]. After 3 months of RTX treatment, all patients had responded, with one patient being in complete remission. After a mean follow-up of 9 months, C-reactive protein concentrations had normalized, peripheral blood eosinophils count decreased, and CS had been reduced in all patients. Within the 9 months observation period, no relapses were recorded [85].

A cohort of 41 patients with EGPA treated with RTX between 2003 and 2013 was subsequently reported. They included new-onset, refractory, and relapsed diseases [83]. At 6 months, 83% of the patients improved, with remission achieved in 34% of them. CS was reduced in all patients and ANCA-positivity at baseline was associated with a higher remission rate [83]. B-cell depletion occurred in all patients. However, there were no differences in eosinophil counts.

Another cohort of 69 patients with refractory EGPA was studied and treated with RTX [87]. Response to treatment was achieved in 40.6% of patients by 6 months and this rose to 77.3% by 24 months. No differences according to ANCA-status were reported. RTX permitted prednisolone dose reductions. However, there were no changes with RTX treatment in the C-reactive protein and peripheral eosinophil counts [87].

Some of the clinical trials that are currently being conducted with RTX are RTX in eosinophilic granulomatosis with polyangiitis (REOVAS, NCT02807103) [90] and maintenance of remission with RTX *vs.* azathioprine for newly-diagnosed or relapsing eosinophilic granulomatosis with polyangiitis (MAINRITSEG, NCT03164473) [91].

Despite the promising results of the studies described above, further prospective, randomized trials evaluating the use of RTX in EGPA are warranted. A summary of all relevant studies with RTX can be found in Table 5.

Table 5. RTX therapy in patients with EGPA

Reference	Study design	Number of patients	Dose and route of administration	Results
Cartin-Ceba et al. [89], 2011	Prospective open-label pilot study	3	375 mg/m^2 every 4 weeks	All patients achieved renal remission
Thiel et al. [85], 2013	Single-center cohort of patients	9	No recorded	CS reduction BVAS reduction C-reactive protein normalized Reduction in blood eosinophil counts No relapses had been recorded
Mohammad et al. [83], 2016	Cohort of patients	41	375 mg/m^2 every 4 weeks (n = 10) 2 doses 1,000 mg (n = 30)	34% Of the patients achieved remission CS reduction in all patients ANCA-positivity at baseline was associated with a higher remission rate at 12 months No differences in eosinophil counts

Table 5. RTX therapy in patients with EGPA (*continued*)

Reference	Study design	Number of patients	Dose and route of administration	Results
Teixera et al. [87], 2019	Cohort of patients	69	-	No differences in treatment response according to ANCA-status CS reductions No changes in blood eosinophil counts

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Anti-complement agents

Studies involving murine models have shown that activation of complement is critical in the pathophysiology of AAV and ANCA-activated neutrophils may activate complement and produce complement component 5a (C5a), these mechanisms may contribute to a worsening of respiratory symptoms [92, 93]. Other murine models have reported that C5-deficient mice and those lacking a C5a receptor (C5aR) did not develop AAV [94, 95] and concluded that blocking the C5aR with a small molecule may improve disease severity.

It was shown in a case report that an anti-C5 antibody (eculizumab) improved renal function [96] and a recent review reported that replacement of CS with a C5aR inhibitor, called avacopan is already a new therapeutic option that may decrease the CS intake and could improve the long-term outcome of patients with AAV. However, most studies are in murine models, and more clinical trials are needed [97].

Conclusions

EGPA remains a challenge for clinicians because the current gold standard treatments, CS and immunomodulators, do not always control symptoms and are often associated with significant morbidity. However, as a rare orphan disease, testing new therapies is challenging because few centers have sufficient numbers of patients to conduct randomised placebo-controlled trials.

Like patients with asthma, it is recommended to must phenotype and endotype patients with EGPA to offer them the best therapeutic alternative. Although there have been great advances in the treatment of EGPA since mepolizumab has been approved by the FDA and the ongoing trials with the new biologic therapies can hopefully be a promising tool for refractory/recurrent EGPA, further studies are needed to demonstrate the long-term efficacy of these novel biologic therapies.

Abbreviations

AAV: antineutrophil cytoplasmic antibodies-associated vasculitis

ACR: American College of Rheumatology

ACT: asthma control test

ANCA: antineutrophil cytoplasmic antibodies

BVAS: Birmingham vasculitis activity score

C5a: complement component 5a

C5aR: complement component 5a receptor

CS: corticosteroids

EGPA: eosinophilic granulomatosis with polyangiitis

FDA: Food and Drug Administration

FFS: Five Factor Score

IL-5: interleukin-5

ISAs: immunosuppressive agents

IV: intravenous

mAb: monoclonal antibody

MPO: myeloperoxidase

RTX: rituximab

SC: subcutaneous

Declarations

Author contributions

ACH: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. CP: Conceptualization, Investigation, Visualization, Writing—review & editing. GP: Validation, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

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References

1. Olivieri B, Tinazzi E, Caminati M, Lunardi C. Biologics for the treatment of allergic conditions: eosinophil disorders. Immunol Allergy Clin North Am. 2020;40:649–65.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised international Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum. 2013;65:1–11.
3. Loughlin JE, Cole JA, Rothman KJ, Johnson ES. Prevalence of serious eosinophilia and incidence of Churg-Strauss syndrome in a cohort of asthma patients. Ann Allergy Asthma Immunol. 2002;88:319–25.
4. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of churg-strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33:1094–100.
5. Grayson PC, Ponte C, Suppiah R, Robson JC, Craven A, Judge A, et al.; DCVAS Study Group. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. Arthritis Rheum. 2022;74:386–92.

6. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009;68:1827–32.
7. Chaigne B, Terrier B, Thieblemont N, Witko-Sarsat V, Mouthon L. Dividing the Janus vasculitis? Pathophysiology of eosinophilic granulomatosis with polyangitis. Autoimmun Rev. 2016;15:139–45.
8. Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, et al. Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): a study of 157 patients by the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and the European Respiratory Society Taskforce on eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Autoimmun Rev. 2017;16:1–9.
9. Raffray L, Guillevin L. Updates for the treatment of EGPA. Presse Med. 2020;49:104036.
10. Rothenberg ME, Hogan SP. The eosinophil. Annu Rev Immunol. 2006;24:147–74.
11. Nappi E, De Santis M, Paoletti G, Pelaia C, Terenghi F, Pini D, et al. New onset of eosinophilic granulomatosis with polyangiitis following mRNA-based COVID-19 vaccine. Vaccines (Basel). 2022;10:716.
12. Bayrak Durmaz MS, Çelebi Sözener Z, Bavbek S. Eosinophilic granulomatosis with polyangitis: a new target for biologicals. Tuberk Toraks. 2022;70:93–101.
13. Erle DJ, Sheppard D. The cell biology of asthma. J Cell Biol. 2014;205:621–31.
14. Nguyen Y, Guillevin L. Eosinophilic granulomatosis with polyangiitis (Churg–Strauss). Semin Respir Crit Care Med. 2018;39:471–81.
15. Hellmich B, Csernok E, Gross WL. Proinflammatory cytokines and autoimmunity in Churg-Strauss syndrome. Ann N Y Acad Sci. 2005;1051:121–31.
16. Marvisi C, Sinico RA, Salvarani C, Jayne D, Prisco D, Terrier B, et al. New perspectives in eosinophilic granulomatosis with polyangiitis (EGPA): report of the first meeting of the European EGPA Study Group. Intern Emerg Med. 2019;14:1193–7.
17. Jakiela B, Szczeklik W, Plutecka H, Sokolowska B, Mastalerz L, Sanak M, et al. Increased production of IL-5 and dominant Th2-type response in airways of Churg-Strauss syndrome patients. Rheumatology (Oxford). 2012;51:1887–93.
18. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin PL; French Vasculitis Study Group (FVSG). The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore). 2011;90:19–27.
19. Chumbley LC, Harrison EG Jr, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. Mayo Clin Proc. 1977;52:477–84.
20. Guillevin L, Jarrousse B, Lok C, Lhote F, Jais JP, Le Thi Huong Du D, et al. Longterm followup after treatment of polyarteritis nodosa and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa. J Rheumatol. 1991;18:567–74.
21. Vega Villanueva KL, Espinoza LR. Eosinophilic Vasculitis. Curr Rheumatol Rep. 2020;22:5.
22. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERAEDTA recommendations for the management of ANC-aassociated vasculitis. Ann Rheum Dis. 2016;75:1583–94. Erratum in: Ann Rheum Dis. 2017;76:1480.
23. Emejuaiwe N. Treatment strategies in ANCA-associated vasculitis. Curr Rheumatol Rep. 2019;21:33.
24. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al.; EGPA Mepolizumab Study Team. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017;376:1921–32.
25. Flood-Page P, Menzies-Gow A, Phipps S, Ying S, Wangoo A, Ludwig MS, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. J Clin Invest. 2003;112:1029–36.
26. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al.; MENSA Investigators.

Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371:1198–207.
27. Nagase H, Ueki S, Fujieda S. The roles of IL-5 and anti-IL-5 treatment in eosinophilic diseases: asthma, eosinophilic granulomatosis with polyangiitis, and eosinophilic chronic rhinosinusitis. Allergol Int. 2020;69:178–86.
28. Highlights of prescribing information [Internet]. Silver Spring: U.S. Food and Drug Administration; c2022 [cited 2022 Sep 16]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761122s000lbl.pdf
29. Keating GM. Mepolizumab: first global approval. Drugs. 2015;75:2163–9.
30. Kahn JE, Grandpeix-Guyodo C, Marroun I, Catherinot E, Mellot F, Roufosse F, et al. Sustained response to mepolizumab in refractory Churg-Strauss syndrome. J Allergy Clin Immunol. 2010;125:267–70.
31. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. J Allergy Clin Immunol. 2010;125:1336–43.
32. Herrmann K, Gross WL, Moosig F. Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome. Clin Exp Rheumatol. 2012;30:S62–5.
33. Steinfeld J, Bradford ES, Brown J, Mallett S, Yancey SW, Akuthota P, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol. 2019;143:2170–7.
34. Caminati M, Crisafulli E, Lunardi C, Micheletto C, Festi G, Maule M, et al. Mepolizumab 100 mg in severe asthmatic patients with EGPA in remission phase. J Allergy Clin Immunol Pract. 2021;9:1386–8.
35. Özdel Öztürk B, Yavuz Z, Aydın Ö, Mungan D, Sin BA, Demirel YS. Effectiveness of low-dose mepolizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): a real-life experience. Int Arch Allergy Immunol. 2022;183:1281–90.
36. Bettiol A, Urban ML, Dagna L, Cottin V, Franceschini F, Del Giacco S, et al.; European EGPA Study Group. Mepolizumab for eosinophilic granulomatosis with polyangiitis: a European multicenter observational study. Arthritis Rheumatol. 2022;74:295–306.
37. Study of mepolizumab-based regimen compared to conventional therapy strategy in patients with eosinophilic granulomatosis with polyangiitis (E-merge) (E-merge) [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Oct 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT05030155?cond=EGPA++Eosinophilic+Granulomatosis+with+Polyangiitis&draw=2&rank=5
38. Mepolizumab long-term study to asses real world safety and effectiveness of eosinophilic granulomatosis with polyangiitis (EGPA) in Japan (MARS) [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Oct 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT04551989?cond=EGPA++Eosinophilic+Granulomatosis+with+Polyangiitis&draw=2&rank=7
39. Long-term access program (LAP) of mepolizumab who participated in study MEA115921 [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Oct 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03298061?cond=EGPA++Eosinophilic+Granulomatosis+with+Polyangiitis&draw=3&rank=15
40. NUCALA® special drug use investigation (EGPA, long-term) [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Oct 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03557060?cond=EGPA++Eosinophilic+Granulomatosis+with+Polyangiitis&draw=3&rank=16
41. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al.; SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;388:2115–27.
42. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al.; CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients

with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, doubleblind, placebocontrolled phase 3 trial. Lancet. 2016;388:2128–41.
43. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al.; ZONDA Trial Investigators. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376:2448–58.
44. Takenaka K, Minami T, Yoshihashi Y, Hirata S, Kimura Y, Kono H. Decrease in MPO-ANCA after administration of benralizumab in eosinophilic granulomatosis with polyangiitis. Allergol Int. 2019;68:539–40.
45. Coppola A, Flores KR, De Filippis F. Rapid onset of effect of benralizumab on respiratory symptoms in a patient with eosinophilic granulomatosis with polyangiitis. Respir Med Case Rep. 2020;30:101050.
46. Colantuono S, Pellicano C, Leodori G, Cilia F, Francone M, Visentini M. Early benralizumab for eosinophilic myocarditis in eosinophilic granulomatosis with polyangiitis. Allergol Int. 2020;69:483–4.
47. Lee Y, Hojjati M. Benralizumab as a potential adjunctive therapy in eosinophilic granulomatosis with polyangiitis. J Clin Rheumatol. 2021;27:S401–2.
48. Carrillo-Martin I, Abril A, Donaldson AM, Gonzalez-Estrada A. An alternative approach against eosinophils for the treatment of eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol Pract. 2020;8:2079–80.
49. Chica-Guzmán MV, Morillo-Guerrero R, Carrón-Herrero A, González-de-Olano D, Almonacid-Sánchez C. Eosinophilic granulomatosis with polyangiitis successfully treated with benralizumab. Ann Allergy Asthma Immunol. 2020;125:228–30.
50. Martínez-Rivera C, Garcia-Olivé I, Urrutia-Royo B, Basagaña-Torrento M, Rosell A, Abad J. Rapid effect of benralizumab in exacerbation of severe eosinophilic asthma associated with eosinophilic granulomatosis with polyangiitis. BMC Pulm Med. 2021;21:35.
51. Bormioli S, Vultaggio A, Nencini F, Comin CE, Bercich L, Bezzi M, et al. Benralizumab: resolution of eosinophilic pulmonary vasculitis in a patient with EGPA. J Investig Allergol Clin Immunol. 2021;31:519–21.
52. Kolios AGA, Lutterotti A, Kulcsar Z, Renner T, Rudiger A, Nilsson J. Benralizumab in eosinophilic granulomatosis with polyangiitis complicated by *Staphylococcus aureus* sepsis. Clin Immunol. 2021;222:108574.
53. Lim AKH, Antony A, Gingold M, Simpson I, Looi WF, MacDonald MI. Emergence of extrathoracic manifestations of eosinophilic granulomatosis with polyangiitis during benralizumab treatment. Rheumatol Adv Pract. 2021;5:rkab033.
54. Miyata Y, Inoue H, Homma T, Tanaka A, Sagara H. Efficacy of benralizumab and clinical course of IgG4 in eosinophilic granulomatosis with polyangiitis. J Investig Allergol Clin Immunol. 2021;31:346–8.
55. Koga Y, Aoki-Saito H, Kamide Y, Sato M, Tsurumaki H, Yatomi M, et al. Perspectives on the efficacy of benralizumab for treatment of eosinophilic granulomatosis with polyangiitis. Front Pharmacol. 2022;13:865318.
56. Padoan R, Chieco Bianchi F, Marchi MR, Cazzador D, Felicetti M, Emanuelli E, et al. Benralizumab as a glucocorticoid-sparing treatment option for severe asthma in eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol Pract. 2020;8:3225–7.E2.
57. Nanzer AM, Dhariwal J, Kavanagh J, Hearn A, Fernandes M, Thomson L, et al. Steroid-sparing effects of benralizumab in patients with eosinophilic granulomatosis with polyangiitis. ERJ Open Res. 2020;6:00451-2020.
58. Guntur VP, Manka LA, Denson JL, Dunn RM, Dollin YT, Gill M, et al. Benralizumab as a steroid-sparing treatment option in eosinophilic granulomatosis with polyangiitis. J Allergy Clin Immunol Pract. 2021;9:1186–93.E1.
59. Benralizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) study (BITE) [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Oct 30]. Available from: https://

clinicaltrials.gov/ct2/show/NCT03010436?cond=EGPA++Eosinophilic+Granulomatosis+with+Polyangiitis&draw=14&rank=23
60. Efficacy and safety of benralizumab in EGPA compared to mepolizumab. (MANDARA) [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Oct 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT04157348?cond=EGPA++Eosinophilic+Granulomatosis+with+Polyangiitis&draw=17&rank=9
61. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3:355–66.
62. Kent BD, d'Ancona G, Fernandes M, Green L, Roxas C, Thomson L, et al. Oral corticosteroid-sparing effects of reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis. ERJ Open Res. 2020;6:00311-2019.
63. Manka LA, Guntur VP, Denson JL, Dunn RM, Dollin YT, Strand MJ, et al. Efficacy and safety of reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis. Ann Allergy Asthma Immunol. 2021;126:696–701.E1.
64. Navinés-Ferrer A, Serrano-Candelas E, Molina-Molina GJ, Martín M. IgE-related chronic diseases and anti-IgE-based treatments. J Immunol Res. 2016;2016:8163803.
65. Basta F, Mazzuca C, Nucera E, Schiavino D, Afeltra A, Antonelli Incalzi R. Omalizumab in eosinophilic granulomatosis with polyangiitis: friend or foe? A systematic literature review. Clin Exp Rheumatol. 2020;38:214–20.
66. 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.
67. Pabst S, Tiyerili V, Grohé C. Apparent response to anti-IgE therapy in two patients with refractory "forme fruste" of Churg–Strauss syndrome. Thorax. 2008;63:747–8.
68. Lau EMT, Cooper W, Bye PT, Yan K. Difficult asthma and Churg-Strauss-like syndrome: a cautionary tale. Respirology. 2011;16:180–1.
69. 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.
70. 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 polyangioitis. Ann Allergy Asthma Immunol. 2018;120:209–11.
71. Jachiet M, Samson M, Cottin V, Kahn JE, Le Guenno G, Bonniaud P, et al.; French Vasculitis Study Group. 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.
72. Celebi Sozener Z, Gorgulu B, Mungan D, Sin BA, Misirligil Z, Aydin O, 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.
73. Puéchal X, Rivereau P, Vinchon F. Churg-Strauss syndrome associated with omalizumab. Eur J Intern Med. 2008;19:364–6.
74. 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.
75. Ruppert AM, Averous G, Stanciu D, Deroide N, Riehm S, Poindron V, et al. Development of Churg-Strauss syndrome with controlled asthma during omalizumab treatment. J Allergy Clin Immunol. 2008;121:253–4.
76. 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.
77. Cisneros C, Segrelles G, Herráez L, Gonzalez A, Girón R. Churg-Strauss syndrome in a patient treated with omalizumab. J Investig Allergol Clin Immunol. 2013;23:504–21.
78. Charles P, Néel A, Tieulié N, Hot A, Pugnet G, Decaux O, et al.; French Vasculitis Study Group. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. Rheumatology (Oxford). 2014;53:532–9.
79. Puéchal X. Therapeutic immunomodulation in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Joint Bone Spine. 2016;83:7–10.
80. Jones RB, Tervaert JWC, Hauser T, Luqmani R, Morgan MD, Peh CA, et al.; European Vasculitis Study Group. Rituximab *versus* cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211–20.
81. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al.; RAVE-ITN Research Group. Rituximab *versus* cyclophosphamide for ANC-associated vasculitis. N Engl J Med. 2010;363:221–32.
82. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al.; RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013;369:417–27.
83. Mohammad AJ, Hot A, Arndt F, Moosig F, Guerry MJ, Amudala N, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg–Strauss). Ann Rheum Dis. 2016;75:396–401.
84. Novikov P, Moiseev S, Smitienko I, Zagvozdkina E. Rituximab as induction therapy in relapsing eosinophilic granulomatosis with polyangiitis: a report of 6 cases. Joint Bone Spine. 2016;83:81–4.
85. Thiel J, Hässler F, Salzer U, Voll RE, Venhoff N. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Arthritis Res Ther. 2013;15:R133.
86. Emmi G, Rossi GM, Urban ML, Silvestri E, Prisco D, Goldoni M, et al. Scheduled rituximab maintenance reduces relapse rate in eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2018;77:952–4.
87. Teixeira V, Mohammad AJ, Jones RB, Smith R, Jayne D. Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. RMD Open. 2019;5:e000905.
88. Casal Moura M, Berti A, Keogh KA, Volcheck GW, Specks U, Baqir M. Asthma control in eosinophilic granulomatosis with polyangiitis treated with rituximab. Clin Rheumatol. 2020;39:1581–90.
89. Cartin-Ceba R, Keogh KA, Specks U, Sethi S, Fervenza FC. Rituximab for the treatment of Churg-Strauss syndrome with renal involvement. Nephrol Dial Transplant. 2011;26:2865–71.
90. Rituximab in eosinophilic granulomatosis with polyangiitis (REOVAS) [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Nov 06]. Available from: https://clinicaltrials.gov/ct2/show/NCT02807103
91. Maintenance of remission with rituximab *versus* azathioprine for newly-diagnosed or relapsing eosinophilic granulomatosis with polyangiitis (MAINRITSEG) [Internet]. Bethesda: National Library of Medicine; c2022 [cited 2022 Nov 06]. Available from: https://clinicaltrials.gov/ct2/show/NCT03164473
92. Wu EY, McInnis EA, Boyer-Suavet S, Mendoza CE, Aybar LT, Kennedy KB, et al. Measuring circulating complement activation products in myeloperoxidase- and proteinase 3-antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol. 2019;71:1894–903.
93. Jennette JC, Xiao H, Falk R, Gasim AMH. Experimental models of vasculitis and glomerulonephritis induced by antineutrophil cytoplasmic autoantibodies. Contrib Nephrol. 2011;169:211–20.
94. Xiao H, Schreiber A, Heeringa P, Falk RJ, Jennette JC. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. Am J Pathol. 2007;170:52–64.
95. Schreiber A, Xiao H, Jennette JC, Schneider W, Luft FC, Kettritz R. C5a receptor mediates neutrophil

activation and ANCA-induced glomerulonephritis. J Am Soc Nephrol. 2009;20:289–98.
96. Xiao H, Dairaghi DJ, Powers JP, Ertl LS, Baumgart T, Wang Y. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol. 2014;25:225–31.
97. Tesar V, Hruskova Z. Complement inhibition in ANCA-associated vasculitis. Front Immunol. 2022;13:888816.