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Vasculitis (C Pagnoux and M Walsh, Section Editors)

Current and Future Treatment Options for Eosinophilic Granulomatosis With Polyangiitis

Alvise Berti, MD[1,2]
Ulrich Specks, MD[2,*]
Karina A. Keogh, MD[2]
Divi Cornec, MD, PhD[2,3]

Address
[1]Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Insititute, Milan, and Santa Chiara Hospital, Trento, Italy
[*,2]Thoracic Disease Research Unit, Division of Pulmonary and Critical Care Medicine, Mayo Clinic Rochester 200, 1st Street, Rochester, MN, 55901, USA
Email: specks.ulrich@mayo.edu
[3]INSERM UMR1227, Lymphocytes B et Autoimmunité, Université de Bretagne Occidentale, CHU de Brest, Brest, France

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Opinion statement

Purpose of review This review aims to give an overview of efficacy and safety of the therapeutic options for eosinophilic granulomatosis with polyangiitis (EGPA).
Recent findings There are few current treatments beyond glucocorticoids for the successful induction and maintenance of remission in EGPA, and glucocorticoids remain the cornerstone of treatment. Life-threatening manifestations likely benefit from the addition of cytotoxic agents, although results of studies investigating cyclophosphamide or azathioprine have shown mixed efficacy results and high adverse event rates. More recently, targeted therapies including rituximab and mepolizumab have shown encouraging results. Since bronchial asthma often persists beyond the control of vasculitis disease manifestations, inhaled respiratory therapy and a multispecialty management approach are advocated.
Summary EGPA has been the subject of very few randomized controlled trials. Glucocorticoids remain the cornerstone of treatment. Among others, evidence of efficacy for mepolizumab and rituximab is accumulating. The optimization of asthma control is recommended.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare systemic necrotizing vasculitis of the small-sized vessels that is characterized by respiratory tract involvement, traditionally occurring in patients with late-onset asthma and peripheral eosinophilia [1]. Anti-neutrophil cytoplasmic antibodies (ANCA) directed against myeloperoxidase (MPO) are detected in approximately 30–45% of the patients with active disease [2] (and up to 75% during active disease) [3] and are useful for the diagnosis of EGPA. Despite features shared with the other ANCA-associated vasculitides (AAV), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA), EGPA is considered as a separate entity, and patients with EGPA were not included in most therapeutic trials conducted in AAV [4••]. EGPA represents about 10–20% of all AAV cases, with a recently reported incidence of 0.4/100.000 and prevalence of 1.8/100.000 population in the USA [5].

The clinical spectrum of EGPA at diagnosis is broad, but the development of vasculitis is almost always preceded by eosinophilic asthma [3, 6, 7]. The main manifestations include peripheral neuropathy (50%); ear, nose, and throat (ENT) signs (50%); skin lesions (40%); lung infiltrates (40%); and cardiomyopathy (15%) [7]. The clinical phenotype of EGPA may be affected by the presence of ANCA [2, 7–10, 11••]. ENT manifestations, peripheral neuropathy, renal involvement, myalgia/arthralgia, weight loss, and alveolar hemorrhage (uncommon) are more frequent in ANCA-positive patients, whereas cardiac manifestations are more common in ANCA-negative individuals [7, 11••, 12]. Furthermore, MPO-ANCA-positive patients are more prone to relapse [7]. The presence of MPO-ANCA seems to reflect a more vasculitic phenotype of EGPA compared to a more eosinophilic one without overt vasculitic manifestations in the absence of ANCA [2, 7–10, 11••]. Nevertheless, the role of ANCA status in the classification of the disease remains controversial, and more recently, a categorization of patients with EGPA merely based on ANCA status (MPO-ANCA-positive versus MPO-ANCA-negative patients) was found to be insufficient to separate patients into groups with and without vasculitis features [11••].

Late-onset bronchial asthma is one of the main clinical challenges of EGPA, usually antedating the vasculitic phase by several years (with an average of about 10 years) [7, 13, 14•]. Most patients have asthma, often with an allergic component as well as nasal polyps [6]. Despite the traditional triad of sequential phases (the allergic phase with asthma/allergic rhinitis/sinusitis, the eosinophilic phase with eosinophilic organ infiltrations, and the vasculitic phase), asthma tends to persist after the vasculitis resolution, often requiring long-term systemic glucocorticoid therapy [6, 13]. Interestingly, the severity of asthma increased 3–6 months before the onset of the systemic manifestations, and approximately half of the patients had persistent airflow obstruction despite inhaled and oral glucocorticoid treatment at last follow-up [14•]. Several studies recently analyzed the persistence of asthma in EGPA patients [14•, 15] and suggested that uncontrolled asthma and persistent airflow obstruction may be present in more than 50% of EGPA patients during partial or complete vasculitis remission.

The diagnosis of EGPA is usually coincident with the development of clinical features of vasculitis. Unlike MPA or GPA, EGPA has been the subject of very few randomized controlled trials and few studies exploring the efficacy of innovative treatment options (Fig. 1). Consequently, clinical management recommendations have been issued mostly based on expert opinion and by extrapolation from studies on other forms of AAV [4••]. Cyclophosphamide (CYC), the traditional standard of care for severe life-threatening AAV, has a high rate of serious adverse events [16–19]. Targeted therapies such as rituximab and mepolizumab have been investigated as alternate agents to treat EGPA in more recent years, with encouraging results [20••, 21]. The objective of this work is to review the efficacy and safety of therapeutic options for EGPA with particular emphasis the vasculitic components, the asthmatic components, or both.

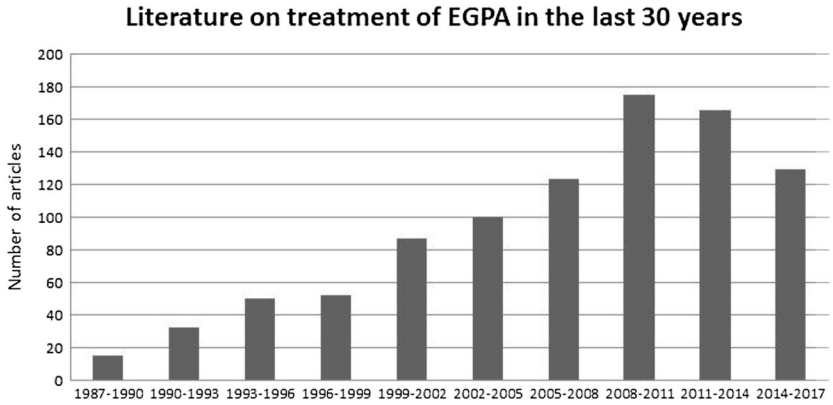

Fig. 1. Number of publications on treatment of EGPA over the last 30 years. The search terms used for this literature search were "eosinophilic granulomatosis with polyangiitis" OR "Churg-Strauss Syndrome" AND "treatment." Data are presented in 3-year intervals.

Treatment of vasculitis in EGPA

Disease-specific recommendations have been developed to diagnose and manage EGPA [4••]. However, the levels of evidence are low, given the lack of randomized control trials (RCTs) specifically conducted in this population (Table 1).

The current treatment paradigm is based on the severity of clinical presentation. Patients with limited or non-severe disease are usually treated with glucocorticoids alone [22], whereas patients with life- or organ-threatening manifestations usually receive additional immunosuppressants such as CYC [19]. Treatment may be guided by the five-factor score (FFS) [23], a tool designed to assess prognosis survival at diagnosis of EGPA, MPA, and polyarteritis nodosa (PAN), which has been subsequently revised with the inclusion of GPA [24]. Of the five items, four [age > 65 years, heart and gastrointestinal involvement (i.e., hemorrhage, infarction, or pancreatitis), stabilized peak creatininemia ≥ 150 μmol/L, each accorded + 1 point] are associated with increased mortality, while the fifth (ENT manifestations) is associated with better outcomes/survival and its absence is scored + 1 [24]. Adjunctive cytotoxic treatments are recommended for a FFS ≥ 1. However, severe manifestations not captured by the FFS include the following: alveolar hemorrhage (rare in EGPA), severe mononeuritis multiplex (common in EGPA), and eye involvement (rare in EGPA) which may also warrant aggressive therapy [4••]. Of note, the presence of mononeuritis multiplex at diagnosis seems to represent a main predictor of the necessity to add an immunosuppressant in patients initially treated with glucocorticoids alone to prevent treatment failure, relapses, and sequelae [25].

Cyclophosphamide

CYC, either intravenous (IV) pulses or daily oral therapy (2 mg/kg/day), is usually used to achieve induction of remission in severe disease. CYC use decreases long-term mortality only in patients with severe disease at presentation [18]. According to published protocols, if pulse administration is chosen, the first three infusions (15 mg/kg or 0.6 g/m^2) should be given every 2 weeks, with a maximum of 1.2 g per infusion, and doses need to be reduced according to renal function. Pulses 3–6 at 15 mg/kg or 0.7 g/m^2 can then be infused every 3 weeks. Oral CYC is usually given for 3–6 months until remission is obtained. In MPA and GPA, oral and pulse CYC have similar efficacy to induce remission, and pulse CYC leads to smaller cumulative doses but may increase the relapse rate compared to oral CYC [16].

Patients aged 65 years or older may benefit from lower CYC doses to avoid drug-related side effects (a maximum of six 500-mg fixed-dose IV CYC pulses, every 2–3 weeks, plus glucocorticoids for ~ 9 months followed by maintenance azathioprine or methotrexate) as shown in EGPA, GPA, and MPA [17]. CYC usage may permanently impair fertility, and therefore, measures to preserve fertility should be considered, including use of an alternate agent, use of lower cumulative doses of CYC, sperm and oocyte harvesting, in vitro fertilization, and the hormone therapy to preserve ovarian function [26] *Pneumocystis jiroveci* pneumonia with prophylaxis is advisable in these patients and should be continued even beyond the discontinuation of CYC for as long as lymphopenia persists [4••, 26].

Rituximab

A growing body of retrospective case series and open-label studies suggests the efficacy of B cell depletion using RTX in patients with severe EGPA with renal involvement [21], and in refractory or relapsing disease [27], especially in MPO-ANCA-positive patients with systemic vasculitis as the predominant clinical manifestation of active disease [28]. In practice, the use of RTX in MPO-ANCA-positive patients with EGPA is sometimes extrapolated from other RCT results conducted in other AAVs [29, 30]. At present, the evidence in support of using RTX for induction or maintenance of remission in EGPA remains soft, and prospective, blinded RCTs are still ongoing (Table 1). RTX can be associated with infusion-related adverse events such as rash, pruritus, rhinitis, fever, chills, bronchospasm, sometimes severe, hypotension, headache, or myalgia which may on rare occasions require the application of desensitization protocols [31, 32]. It can also rarely induce severe hypogammaglobulinemia in AAV patients with an increased risk of infectious complications [33]. Patients who have received CYC prior to treatment with RTX are at particular risk for hypogammaglobulinemia [34, 35].

Two RCTs have been designed to test the efficacy and safety of RTX in EGPA and are still ongoing (Table 1). The REOVAS study (Clinicaltrials.gov: NCT02807103) plans to include 108 patients with new diagnosis or relapsing and active disease (BVAS ≥ 3) who will be randomized to receive RTX (two 1-g infusions, experimental group) or a conventional therapeutic strategy based on FFS-assessed disease severity (comparative group). The study aims to evaluate both the efficacy of RTX to induce remission and its role as glucocorticoid-sparing agent at 1 year. The MAINRITSEG study (Clinicaltrials.gov:

Table 1. Published or ongoing multicentric, placebo-controlled RCTs in EGPA

Name of the study, drug tested, number of patients, status	Inclusion criteria	Study arms Primary (PE) and secondary (SE) endpoints	Study start date and estimated year of completion	Reference
REOVAS Rituximab for remission induction *N* = 108 Recruiting	Newly diagnosed or relapsing active (BVAS ≥ 3) EGPA, stratified on ANCA, relapsing, and severity, less than 21 days after starting 1 mg/kg prednisone	Study arms: rituximab (two 1000 mg infusions) and glucocorticoids versus glucocorticoids alone for non-severe disease or glucocorticoids + cyclophosphamide for severe disease. PE: proportion of complete remission at 6 months (BVAS 0 and prednisone ≤ 7.5 mg/day) SE: glucocorticoid-sparing efficacy and asthma control at 1 year.	2017–ongoing	NCT02807103
MAINRITSEG Rituximab for remission maintenance *N* = 98 Not recruiting	Newly diagnosed or relapsing EGPA, within 30–300 days following vasculitis remission (BVAS = 0) achieved using RTX or cyclophosphamide for severe disease or glucocorticoids alone for non-severe disease	Study arms: rituximab (four 500 mg infusions every 6 months) versus azathioprine 2 mg/kg/day for 24 months PE: total duration of remission (BVAS = 0 and prednisone ≤ 7.5 mg/day) over 28 months SE: relapse rate, asthma control, glucocorticoid-sparing effect, tolerance	2017–ongoing	NCT03164473
MIRRA Mepolizumab for remission maintenance *N* = 130 Completed (published)	Relapsing or refractory EGPA receiving standard of care therapy including background glucocorticoid (stable dose ≥ 7.5 mg/day) therapy with or without immunosuppressive therapy, with the exclusion of the patients with organ (creatinine > 513 µmol per liter) or life-threatening disease	Study arms: mepolizumab (300 mg every 4 weeks, subcutaneous) versus placebo over 52 weeks. Pre-specified steroid tapering schedule. PE: accrued number of weeks of complete remission (BVAS = 0 and prednisone ≤ 4 mg/day) and proportion of subjects in remission at both weeks 36 and 48 SE: vasculitis or asthma relapse, glucocorticoid-sparing effect, tolerance	2014–2016	NCT02020889

NCT03164473) aims to assess the effect of RTX compared to AZA maintenance therapy on the duration of remission. In this trial, subjects will be randomized to either RTX maintenance therapy (4 fixed-dose RTX infusions of 500 mg every 6 months) or AZA (2 mg/kg/day for 24 months), associated with the corresponding placebo, after achievement of remission.

Azathioprine

The recently published RCTs "azathioprine versus placebo in Microscopic Polyangiitis, Polyarteritis Nodosa or Eosinophilic Granulomatosis With Polyangiitis" (CHUSPAN2) [36••] aimed to assess whether the addition of AZA or placebo to glucocorticoids for remission induction in patients with non-severe patients disease proves beneficial. Notably, 51 out of 95 patients who met the inclusion criteria had EGPA. At 2 years, the addition of AZA to glucocorticoids compared to only glucocorticoids for remission induction did not lower the absolute risk of treatment failure or relapse in EGPA. Furthermore, no benefit of AZA on asthma, nasal or sinus disease exacerbations, or glucocorticoid sparing was demonstrated. While no apparent benefit of AZA was identified in this exploratory subset analysis of patients with non-severe EGPA, it is questionable whether there was enough power to exclude any benefit of AZA (or any other DMARDs) with a high level of confidence. No study has specifically addressed the use of DMARDs (including AZA) for EGPA maintenance therapy, and their use in this disease is mainly extrapolated from RCTs conducted in GPA and MPA [37, 38] or by open-label RCTs including EGPA along with other AAV [17].

Mycophenolate mofetil

The off-label use of mycophenolate mofetil (MMF) may have a role as a steroid-sparing agent and may be an option in EGPA. Its use has been supported by several case reports [39–41] and a small open-label study including EGPA patients among other AAV patients [42]. However, caution may be advisable, given the risk of serious adverse events [39].

Methotrexate

Although there is no clear evidence for EGPA, methotrexate (10–30 mg/week, along with folic acid replacement, 10–30 mg/week) may be used as a potent remission-maintenance agent for AAV in general [37]. The optimal duration of maintenance therapy remains unknown and 18–24 months following remission induction could be recommended [4••].

Intravenous immunoglobulins

Scarce evidence exists for the use of IV immunoglobulins (IVIg) in EGPA. According to guidelines [4••], IVIg can be considered as second-line therapy for patients on glucocorticoids (and/or other immune-suppressants) with EGPA flares refractory to other treatments or during pregnancy or in the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections. Several case reports and case series support the efficacy of high-dose IVIg (i.e., 2 g/kg for 2–5-day cycles which can be repeated every 3–4 weeks) in naïve and previously treated EGPA patients [43, 44], especially in the case of cardiac and/or peripheral neuropathic involvement [45]. Treatment with IVIg showed successful results in pregnant patients, a condition that could be challenging

when unresponsive to glucocorticoids and/or azathioprine [46]. Finally, a complete clinical and functional recovery with a long-term stable remission and a low incidence of side effects has been achieved by the association of intravenous IVIg with plasmapheresis in a small case series [47].

Interferon-alpha

Although interferon-alpha achieved acceptable remission rates in a small, prospective, open-label observational study [48], long-term outcomes were affected by relapses or adverse events, leading to frequent discontinuation of this drug [49, 50]. Therefore, this treatment is not recommended as a first line therapy [4••].

Plasma exchanges

Although generally not effective in EGPA [51, 52], it could be considered for ANCA-positive patients with alveolar hemorrhage, rapidly progressive glomerulonephritis, or both when unresponsive to other treatments [4••, 53]. However, current available data do not support its routine use.

Treatment of asthmatic manifestations

The main challenge in the long-term treatment of patients with EGPA is to avoid long-term exposure to oral glucocorticoids which are often necessary to control asthma, rhinosinusitis, or nasal polyposis long after the manifestations of vasculitis have been put into remission. Symptoms of bronchial asthma may decrease as the vasculitic phase ensues [14•, 54], but the relationship between the natural history of asthma and polyangiitis remains still obscure. Several reports have highlighted that EGPA can be unmasked when glucocorticoids sparing agents, such as leukotriene-receptor antagonists (LRA) [3] or omalizumab [55], are introduced into the management of patients with eosinophilic asthma uncontrolled by glucocorticoids alone. Yet, those agents have been also used to control asthmatic manifestations of EGPA when vasculitis has been successfully put into remission [56, 57].

Inhaled glucocorticoids and bronchodilators

In one study, only half of EGPA patients received regular therapy with inhaled medication for asthma and only those with nasal polyps (but not those with rhinitis or chronic rhinosinusitis without nasal polyps) received topical nasal therapy, in addition to systemic immunosuppressant and oral glucocorticoid treatment [15], often leading to high cumulative doses of glucocorticoid [15, 58]. Respiratory manifestations are thus frequent issues for patients with EGPA, and inhaled therapy for asthma is arguably poorly managed by treating physicians. Optimizing the management of the non-vasculitic respiratory manifestations of EGPA is a main objective when treating a patient.

Although specific recommendations for asthma treatment in EGPA were not included in the published guidelines [4••], a stepwise approach to treatment which tries to implement the use of inhaled drugs and to minimize the systemic glucocorticoid exposure is advisable. Global Strategy for Asthma Management and Prevent (GINA) guidelines aim to achieve good control of asthma

symptoms and minimize future risk of exacerbations (Global strategy for asthma management and prevention. Update 2014. Available from: www.ginasthma.org), which could be pursued in EGPA asthma as well. Briefly, a low dose of inhaled glucocorticoids along with avoidance of environmental triggers (e.g. smoking) may be considered in milder cases (steps 1–2 of pharmacotherapy), with a short acting beta-2 agonist as rescue inhaler as needed. For cases of moderate asthma (steps 3–4), adding a long acting beta-2 agonist eventually with a medium/high dose of inhaled glucocorticoids is recommended, reserving the systemic glucocorticoid or other treatment such as mepolizumab only for more severe cases (step 5). Tiotropium or leukotriene-receptor antagonists may be added starting from step 4. Nevertheless, asthma often remains poorly controlled in EGPA and glucocorticoid dependent in a sizable number of patients [15].

Leukotriene-receptor antagonists

Several early series have suggested that leukotriene-receptor antagonists could trigger or cause EGPA [59]. However, a pathogenic role for leukotriene-receptor antagonists in the development of EGPA was not noted subsequently in larger cohorts [3]. EGPA onset after starting a leukotriene-receptor antagonist might be coincidental to EGPA worsening or as a result of glucocorticoid-tapering unmasking symptoms [3].

Omalizumab

Omalizumab is a subcutaneous humanized anti-IgE monoclonal antibody which has been reported to be beneficial and safe in the management of moderate-severe EGPA-related asthma in small case series [56]. Clinical improvement and reduction in the peripheral eosinophil count have been reported in two patients with refractory, *formes frustes* variants of EGPA treated with monthly, lose dose of omalizumab for 18 months [60]. Its off-label use remains questionable given the increased risk of severe flares related to its glucocorticoid-sparing effect for EGPA with asthmatic and/or sinonasal manifestations [55, 61].

Treatments effective for both vasculitic and asthmatic manifestations

Systemic glucocorticoids

The pivotal EGPA treatment is systemic glucocorticoids, effective on the vasculitis manifestations (given their immunosuppressive properties) as well as on the asthmatic ones (given their anti-inflammatory properties). The overwhelming majority of patients with EGPA is thus treated with systemic glucocorticoids [13].

Dosage depends on the severity of the disease, and high doses (~ 1 mg/kg/day prednisone or equivalents) should be reserved for more severe disease, with internal organ involvement or FFS > 0. When life-threatening symptoms are present, starting with methylprednisolone pulses (7.5–15 mg/kg/day) is advised, according to published recommendations [4••]. In the CHUSPAN study, treatment of FFS = 0 EGPA and PAN patients with glucocorticoids alone was effective, achieving a 5-year survival rate of 96.8% [4••, 62]. Eventually, one

third of the patients (especially if affected with peripheral neuropathy) required a cytotoxic agent, suggesting the benefit of early additional immunosuppression [25]. After remission is obtained, low-dose maintenance glucocorticoids are often required to prevent relapses and should be tailored to each patient. A recent retrospective cohort of FFS = 0 EGPA patients, who could not have their prednisone dose lowered to 7.5 mg/day after 3 months due to systemic manifestations and/or refractory asthma and who received additional immunosuppressants, showed that these patients had low relapse rates and did not develop a high rate of serious infection [58].

Mepolizumab

Mepolizumab is a humanized anti-interleukin (IL)-5 monoclonal antibody, with proven efficacy in eosinophilic asthma [63]. Several case reports and two open-labeled studies [64, 65] suggested its efficacy in patients with refractory or relapsing EGPA [66], providing the rationale to target IL-5, the major eosinophil survival factor.

The results of the MIRRA study, the first RCT ever organized in EGPA, were recently published [20••] (Table 1). This double-blinded RCT investigated the

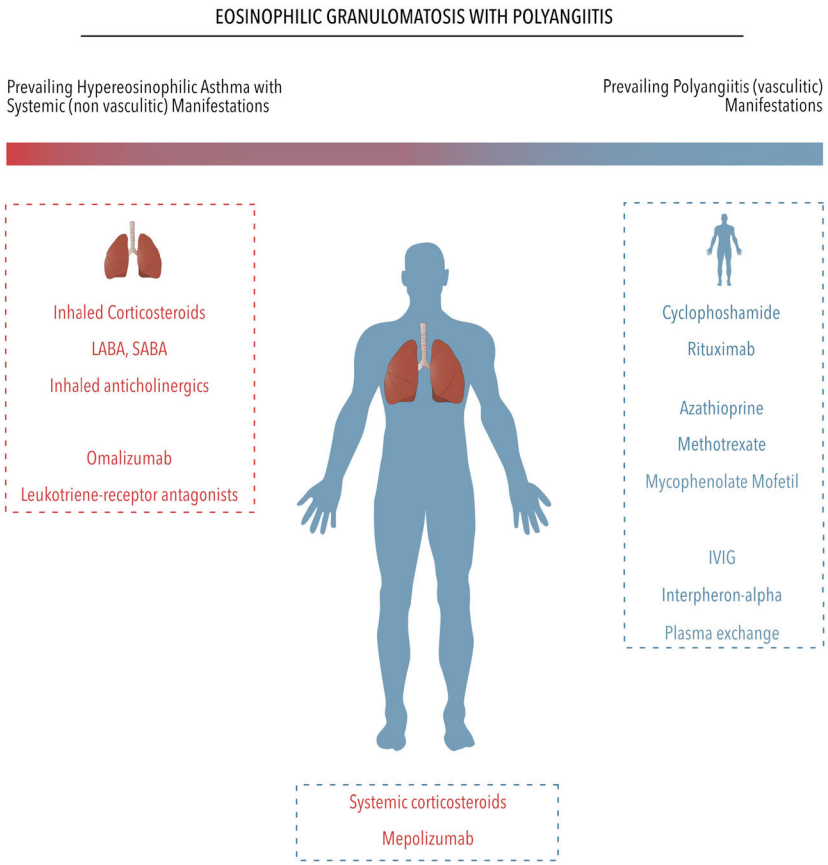

Fig. 2. Overview of the therapeutic options for EGPA related to its clinical spectrum. Current evidence suggests classifying EGPA patients as having predominantly vasculitis versus predominantly eosinophilic asthma with systemic symptoms: different therapeutic agents have different targets.

efficacy and safety of 300 mg mepolizumab, given subcutaneously every 4 weeks, compared with placebo over a 52-week period, in subjects with relapsing or refractory EGPA who had received treatment for at least 4 weeks and were taking a stable glucocorticoid dose (prednisolone or equivalents ≥ 7.5 mg/day). Patients treated with mepolizumab were in remission significantly longer than those receiving placebo (odds ratio 5.9, 95% CI 2.68–13.03), and a higher proportion of participants were in remission compared to placebo at 36 and 48 weeks (odds ratio 16.74, 95% CI 3.61–7.56), thus allowing for reduced glucocorticoid use. Nevertheless, only half the participants treated with mepolizumab achieved protocol-defined remission.

Despite this largely positive result, several questions remain. Is mepolizumab to be considered effective in EGPA vasculitis, or is it more a treatment for eosinophilic asthma of EGPA? Current evidence suggests the classification of EGPA patients in two categories: the phenotype with predominant vasculitis and the phenotype with predominant eosinophilic asthma with systemic symptoms (Fig. 2). Whether mepolizumab is similarly effective in both phenotypes remains unclear. The MIRRA trial considered both vasculitis and asthma flares as relapses, but the asthmatic flares were overall much more frequent than the vasculitic ones. Moreover, only 10% of patients were MPO-ANCA positive in this study, and patients were not required to have active classic vasculitic features at inclusion. Finally, the protocol allows the use of inhaled glucocorticoids overhead and thus likely their use for milder asthma flares, as usually done in clinical practice. Further studies are needed to clarify these points.

Conclusion

In summary, most of the therapeutic approaches explored so far rely on studies conducted in relatively small cohorts of patients with EGPA. Glucocorticoids remain the cornerstone of treatment, and life-threatening manifestations likely benefit from addition of cytotoxic agents. Besides the treatment of vasculitis manifestations, asthma in EGPA often remains a long-term management challenge representing the main cause of long-term high-cumulative glucocorticoid doses. Inhaled respiratory therapy and multispecialty management are therefore advised. There is a paucity of RCTs at this time evaluating a role for biological agents in EGPA. The recently published trial on mepolizumab is encouraging, although several questions regarding optimal application of this evidence into general practice remain. Although RTX efficacy in EGPA has been suggested by several cohort studies, prospective double-blinded trials on subjects treated with RTX are still ongoing.

Compliance with Ethical Standards

Conflict of interest

Dr. Keogh reports grants and non-financial support from GSK, personal fees from BMJ, personal fees from Elsevier Inc, grants from Agency for Healthcare Research and Quality (AHRQ), outside the submitted work.

Alvise Berti declares that he has no conflict of interest.
Ulrich Specks declares that he has no conflict of interest.
Divi Cornec declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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