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POINTS OF VIEW

New perspectives in eosinophilic granulomatosis with polyangiitis (EGPA): report of the first meeting of the European EGPA Study Group

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Abstract
The European Eosinophilic Granulomatosis with Polyangiitis (EGPA) study group first gathered in Firenze in December 2018. The discussion was centred around the clinical and therapeutic needs in EGPA which still remain unmet. Indeed, EGPA is a puzzling and rare disease which shares clinical features with other anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAVs) and hypereosinophilic syndromes (HESs). Some of the recommendations published in 2015 are based on data derived from EGPA-related diseases, rather than from EGPA itself, and therefore need to be updated. Thus, the aim of the meeting was to stimulate ongoing research, to promote collaborative European studies and to define the main issues on which future studies should be focused. Current fields of research on EGPA include potential serological biomarkers of disease activity and of specific organ involvement, possible links between different genetic variants and clinical phenotypes, and new therapeutic perspectives. Herein, we give an overview of the meeting with the goal to stimulate an international collaboration and new points of discussion.

Keywords Eosinophilic granulomatosis with polyangiitis · Vasculitis · ANCA · Rituximab · Mepolizumab · Eosinophils

Background

Eosinophilic granulomatosis with polyangiitis (EGPA, Churg–Strauss syndrome) is a systemic necrotising vasculitis characterised by asthma and blood and tissue eosinophilia [1]. It belongs to the spectrum of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), despite the fact that ANCA positivity is found in 30–40% of EGPA patients and is much less frequent than in other AAVs [2]. EGPA also shares characteristics with hypereosinophilic syndromes (HES), especially eosinophil infiltration, which contributes to organ damage along with vascular inflammation [3].

In 2009, the European League against Rheumatism (EULAR) first published recommendations for the management of AAVs that also became the standard care for EGPA [4]. Nevertheless, the heterogeneous clinical picture of EGPA led to the need for specific guidelines for diagnosis and management [5]. In 2015, the EGPA Consensus

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Task Force published the recommendations for evaluation and management of EGPA [6]. The authors pointed out that some recommendations had a low level of evidence. A group of European experts was then formed and called European EGPA study group. The participants were invited to discuss different points of interest, as reported in Table 1.

Report

The first meeting of the European EGPA study group was held in Firenze on November 30th and December 1st, 2018. The aim of this meeting was to create a collaborative multidisciplinary group, to define the clinical and therapeutic needs that remain unmet and to promote collaborative European research projects. The group involved European experts on EGPA (mainly rheumatologists, nephrologists, internists, pulmonologists and immunologists), and was endorsed by the European Vasculitis Society (EUVAS) and the French Vasculitis Study Group (FVSG). The first session was dedicated to the "state of art" in EGPA.

Augusto Vaglio (Firenze) discussed the immunopathogenesis and biomarkers in EGPA. A genome-wide association study (GWAS) that has been recently completed demonstrated 11 variants associated with EGPA as a whole, only one with ANCA positivity (HLA-DQ) and two with ANCA negativity (GPA33 and IL-5) (Lyons et al. unpublished). Potential triggers of the disease are still to be clarified.

The pathogenic model is based on a complex cross-talk between humoral and cellular immunity. Eosinophils appear to be the key cells causing tissue damage, but also T and B cells play a role. Some of these cellular pathways have been recently targeted by specific therapies. Rituximab (RTX), by depleting B cells, is capable of inducing remission even in relapsing and refractory EGPA, particularly in ANCA-positive patients [7]. Interleukin-5 (IL-5) regulates eosinophil proliferation and differentiation. Mepolizumab, a humanised monoclonal antibody that targets IL-5, is indicated for the treatment of severe eosinophilic asthma. Recently, mepolizumab has also proved effective in reducing eosinophil-driven manifestations of EGPA [8].

Table 1 Main points discussed during the meeting

Immunopathogenetic model of EGPA
Clinical and prognostic significance of ANCA status
Biomarkers
Cardiac involvement and other life-threatening manifestations
Issues in the definition of remission and relapse in EGPA
Therapeutic options and ongoing RCTs

EGPA eosinophilic granulomatosis with polyangiitis, *ANCA* anti-neutrophil cytoplasm antibody, *RCTs* randomised controlled trials

An important issue that still remains is the lack of diagnostic or prognostic biomarkers in EGPA. No biomarkers are available to assess disease activity, predict the risk of relapse or differentiate chronic *sequelae* of vasculitis from disease flares. The serum levels of IgG4, eotaxin-3 and periostin did not reliably discriminate between active and inactive disease, even if their serum levels were found to be higher at EGPA onset [9].

Renato Alberto Sinico (Milano) focused on ANCA status and its significance for the management and outcome of EGPA. ANCA-positive patients present more frequently with vasculitic symptoms (e.g., glomerulonephritis, neuropathy), whereas ANCA-negative patients are at risk for other (generally eosinophil-driven) complications such as cardiomyopathy [2]. These two clinical subsets show a different genetic background already in the earliest genetic studies based on a candidate gene approach: HLA-DRB4 was associated with an increased risk to develop ANCA-positive EGPA, whereas variations of the *IL-10* gene were a risk factor for ANCA-negative forms [10, 11]. From a prognostic point of view, the presence of ANCA may indicate a higher risk of relapse, whereas survival probability seems to be poorer in ANCA-negative patients. The increased mortality in ANCA-negative patients could be related to the more severe heart involvement. Nevertheless, clinical manifestations and not the ANCA status should dictate the choice of immunosuppression in both induction and maintenance phases.

The whole group of experts discussed the definitions of remission and relapse. Remission was previously defined by the EGPA task force [6] as the absence of any active systemic manifestation (excluding asthma and/or ear, nose and throat) in patients receiving a prednisone dose equal to or lower than 7.5 mg/day. On the other hand, in the MIRRA trial a dose of prednisone of 4 mg/day or less was required to define remission [8]. Relapse was defined by the EGPA task force as the new appearance or recurrence or worsening of clinical EGPA manifestation(s) (excluding asthma and/or ENT), requiring the addition, change or dose increase of glucocorticoids and/or other immunosuppressants [6]. This definition is also not universal, therefore the group concluded that further discussion should take place to develop homogeneous definitions of these outcomes.

Therapeutic options were outlined by Giacomo Emmi (Firenze) and Benjamin Terrier (Paris). Conventional induction treatments are tailored on patients' prognosis. A Five Factor Score (FFS) > 0 and the presence of life- or organ-threatening manifestations is associated with a poor prognosis [6]. In these cases the addition of an immunosuppressant [e.g., cyclophosphamide (CYC)] to glucocorticoids (GCs) is advisable, whereas GCs alone are preferred if there are no severe clinical manifestations and when the FFS is 0 [6].

Alternative therapies are lacking for induction of remission. Intravenous immunoglobulins (IVIgs) were rarely used in refractory cases and in particular conditions, such as pregnancy. Plasmapheresis and Interferon-α were used in selected patients [6]. Maintenance therapy with Methotrexate (MTX) or Azathioprine (AZA) is used in most cases of EGPA after the achievement of remission [6]. Regardless of which induction regimen is chosen, EGPA patients are usually exposed to a high cumulative dose of GCs and remain at high risk of disease-related (especially asthma and ENT manifestations) and treatment-related sequelae.

As in other autoimmune diseases, new therapeutic options include biologic treatments. A personalised management based on clinical phenotype is maybe the future, but is still to be defined. To date, mepolizumab is the most effective treatment for asthma and other eosinophilic manifestations, demonstrating a significant steroid-sparing effect also in EGPA patients [8]. In the recent "MIRRA" trial on patients with relapsing or refractory EGPA, mepolizumab given at the dose of 300 mg every 4 weeks was shown to be effective at inducing clinical remission [8]. However, only approximately half the trial participants treated with mepolizumab had protocol-defined remission. Moreover, in the MIRRA trial a high risk of relapse was seen after mepolizumab discontinuation [8]. Recently, Dupilumab (a blocker of the IL-4 receptor, also able to interfere with IL-13 signalling) and Tezepelumab (a human monoclonal antibody specific for the epithelial cell-derived cytokine thymic stromal lymphopoietin [TSLP]) have shown efficacy in treating severe asthma [12, 13]. However, no data are available in EGPA for both drugs.

The subsequent sessions of the meeting were dedicated to study proposals and ongoing research. Fabian Arndt (Bad Bramstedt) discussed the utility of serum IgG4 levels. IgG4 seems to be stable and easily detectable and could be useful to determine possible associations with particular organ manifestations.

Allyson Egan (Cambridge) focused on the possibility to evaluate the efficacy of mepolizumab in the management of heart involvement. Cardiac disease remains the major cause of death and a predictor of poor long-term prognosis in EGPA. Acute left ventricular dysfunction, myocardial ischemia and arrhythmia are the main clinical features and may ultimately lead to restrictive or dilated cardiomyopathy. Histological findings in patients who underwent heart transplantation showed an eosinophilic-rich infiltration of the myocardium even in patients who were thought to be in remission [14]. Mepolizumab could be a good option, but there are still some points which need to be clarified like the correct dosage, the need for other adjuvant therapies and the clinical assessment of response. Another important issue is the lack of biomarkers to identify patients at risk to develop heart involvement.

Benjamin Terrier presented the ongoing therapeutic trials conducted by the FVSG. In these trials, remission is defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and a prednisone dose < 7.5 mg/day. The REOVAS trial (ClinicalTrials.gov NCT02807103) is a prospective, randomised, double-blind study which compares RTX and conventional treatments in the induction of remission both in newly diagnosed and relapsing EGPA. MAINRITSREG (ClinicalTrials.gov NCT03164473) is also a prospective, randomised, double-blind trial, which evaluates the maintenance of remission and the steroid-sparing effect of RTX versus AZA. The trial enrols patients with newly diagnosed EGPA or with flare within the previous year. Patients are evaluated during the 30–300 days following remission. Finally, the EMERGE trial assesses prospectively the steroid-sparing effect of mepolizumab versus conventional treatments and will start enrolling by the end of 2019. The primary objective of this study is to determine the percentage of patients who achieve a daily dose of prednisone of 4 mg or less.

Future studies on pathogenic aspects of EGPA were discussed by the group.

The role of innate lymphoid cells type 2 (ILC2) in allergic inflammation and chronic rhino-sinusitis with polyps was outlined by Benjamin Terrier. These cells are stimulated by various cytokines, including the epithelial-derived IL-25, IL-33 and TSLP and are critical for eosinophil homeostasis. ILC2 concentrations are high both in the blood and in the broncho-alveolar lavage (BAL) of patients affected by severe and cortico-dependent asthma. These cells could also play a role in EGPA. Preliminary data have shown an increase in ILC2 concentrations in the blood of active EGPA and correlate with the circulating eosinophil counts [15]. Dr Terrier's proposal was to assess the levels of ILC2 in the blood of active and inactive EGPA and to clarify their pathogenetic role.

Augusto Vaglio proposed an integration of GWAS with epigenetic studies. Epigenetics investigate the diverse patterns of modification in the expression of disease-associated genes. A mapping of DNA methylation in patients affected by systemic lupus erythematosus showed a regulatory role in the phenotypic expression of the disease [16]. In EGPA, the methylation patterns could be evaluated within a whole genomic approach using T, B and other immune cells.

Fabian Arndt proposed a study aiming to clarify the role of clonally expanded T cells in EGPA. Based on preliminary data, he highlighted the possibility to identify associations between clinical subsets and the presence of particular TCR rearrangements.

Renato Alberto Sinico and his research group observed that myeloperoxidase (MPO)-ANCA in EGPA patients show an atypical cytoplasmic fluoroscopic pattern, which overlaps with the perinuclear one when tested on ethanol-fixed neutrophils [2]. They confirmed such findings

using different substrates and comparing sera from EGPA patients with those from other AAVs. Sinico's study proposal was to better characterise these particular ANCAs. To find the responsible epitope, his group would use MPO-capture ELISA, a new procedure that captures the antigen bound to a monoclonal antibody. This antibody is a mouse anti-MPO that is known to give a C-ANCA pattern. This should be investigated on large EGPA cohorts, to better identify these epitopes and their pathogenetic role.

Giacomo Emmi proposed a study on the efficacy and safety of mepolizumab in real clinical practice. In particular, the proposed study would aim at comparing the efficacy and safety of mepolizumab 300 mg/4 weeks (the dose used in the randomised MIRRA trial) vs 100 mg/4 weeks (the dose used in asthma and currently used in clinical practice for most EGPA patients treated outside clinical trials). This study will include patients with relapsing and refractory EGPA. The primary end-point will be the proportion of patients that achieve complete remission, defined as a BVAS = 0 and GC dosage < 4 mg daily. The secondary end-points will be the time to first relapse and the frequency and severity of adverse effects.

A further study proposal, outlined by Anna Kernder (Düsseldorf), aims at the creation of an EGPA biobank. The samples' collection will include body fluids and tissue specimens. The biobank will be a practical tool for genetic studies and for the evaluation of new potential biomarkers.

With regards to biomarkers, Juliane Mahrhold (Kirchheim) proposed new parameters that are involved in the biologic action of novel drugs. Among these is the serum B cell-activating factor (BAFF), which is important for B-cell survival and is targeted by belimumab [17]. Additional potential biomarkers include the soluble interleukin 2 receptor (sIL-2r) and the eosinophil cationic protein (ECP), whose association with disease activity is being investigated [18, 19]. Recently, the detection of ANCAs in the sputum of both ANCA-negative and ANCA-.positive patients has been described and could become a new tool in the diagnostic work-up [20].

Conclusions

The final group discussion underlined that several issues need to be addressed. In summary, there is an urgent need to update the current recommendations on EGPA. In particular, remission and relapse in EGPA need to be better defined. Indeed, the characterisation of activity or inactivity of the disease tends to vary among different clinical trials, leading to a more difficult comparison. Moreover, in clinical practice one of the major difficulties is to discriminate remission, relapse and active vasculitis vs treatment sequelae. In this context, a clear nomenclature is required.

Real-life clinical studies are necessary to clarify the real effectiveness and safety of biologic treatments already tested in randomised clinical trials. Finally, reliable biomarkers need to be studied, to better achieve an early diagnosis of EGPA, to detect patients at risk of life-threatening manifestations (such as heart disease) and to differentiate EGPA from other HESs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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