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Editorial

Therapeutic immunomodulation in eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) [1]. EGPA has distinct features, namely asthma, common rhino-sinusal involvement, hypereosinophilia, tissue infiltration with eosinophils and necrotizing granulomatosis vasculitis [2–4].

Conventional immunosuppressive therapy and glucocorticoids have been GPA and MPA standard of care for remission-induction and maintenance for four decades. This regimen has transformed the outcome from death to a strong likelihood of disease control and temporary remission. However, most patients have recurrent relapses that lead to damage and require repeated treatment. Cumulative side effects of immunosuppressive agents and glucocorticoids thus remain major causes of long-term morbidity, damage and death.

The development of therapeutic immunomodulation in systemic autoimmune diseases has shed new light on these complex diseases [5]. Rituximab, an anti-CD20 monoclonal antibody that depletes B-cells in peripheral blood, has been shown to be not inferior to cyclophosphamide to induce remission in severe GPA and MPA patients, with an acceptable safety profile, leading to its registration by the EMA and FDA as drug remission-induction therapy in these patients [6–8]. In addition the MAINRITSAN trial, conducted by the French Vasculitis Study Group, demonstrated that 500 mg rituximab given every 6 months for 18 months was significantly more effective than azathioprine standard of care to maintain remission in severe GPA and MPA, with a similar profile of tolerance [9]. Such therapeutic immunomodulation has changed the standard of care for maintenance therapy in these vasculitides.

Patients with EGPA were excluded from these pivotal trials because this vasculitis is rarer and positive ANCA tests are less frequent than in other ANCA-associated vasculitides. In a long-term analysis of randomized trials of 118 EGPA patients, we have reported that only 29% of patients achieved long-term remission and that relapses occurred in more than 40% of patients, leading to high cumulative morbidity and damage [3]. Moreover, most of these patients cannot be weaned of corticosteroids due to asthma and rhino-sinusal ongoing manifestations, even after vasculitis remission. Their long-term outcome remains to be improved.

In *Joint Bone Spine*, Novikov et al. described their experience of off-label use of rituximab in a case series of 6 patients, of whom 5 had relapsing EGPA [10]. Complete remission was achieved in 4 patients at 6 months with an acceptable toxicity profile but severe side effects were observed in 3 patients. The patients received different schema of rituximab induction therapy in link with the retrospective design and one also received rituximab as maintenance therapy. The authors should be congratulated for their pioneer work and therapeutic evaluation of this rare disease.

Progress has been made in the assessment of EGPA vasculitis activity and of rhino-sinusal manifestations. Novikov et al. have used the EULAR expert recommendations for definition of remission, which should include a prednisone dose $\leq$ 7.5 mg/day [11]. It is now recognized in EGPA that ear, nose and throat (ENT) manifestations and/or asthma flares may not necessarily reflect vasculitis activity [2,3]. The EGPA Task Force recently proposed that the definition of remission in EGPA do not include the control of asthma and/or ENT manifestations [12]. These symptoms should be monitored separately and results should be given beside the evaluation of the vasculitis activity.

EGPA is classically considered a TH2-mediated disease with an activated and skewed T-cell balance (Fig. 1) [13]. EGPA patients T-cells can produce high levels of TH2-associated cytokines such as IL-4 and IL-13 [14]. IL-5 is also up-regulated in active EGPA and is particularly essential for eosinophil activation, maturation and survival. However, the clinical phenotype cannot be explained by an isolated exaggerated TH2 response [4]. Th1 and Th17 cells are also implicated and secrete high amounts of IL-17A in the late phases of the disease [4,14]. Moreover, several lines of evidence also point to a role of B lymphocytes and humoral responses as further contributing to EGPA pathogenesis. Increase in the levels of activated and memory B-cells have been found in active EGPA [15]. Myeloperoxidase (MPO)-pANCA are present in 40% of untreated patients [2]. Patients with EGPA flares often had increased levels of total serum IgE and IgE-containing immune complexes [16], initially supported the hypothesis that EGPA might be an allergy-induced, immune complex vasculitis. Elevated serum IgG4 have also been common features and the switch towards IgG4

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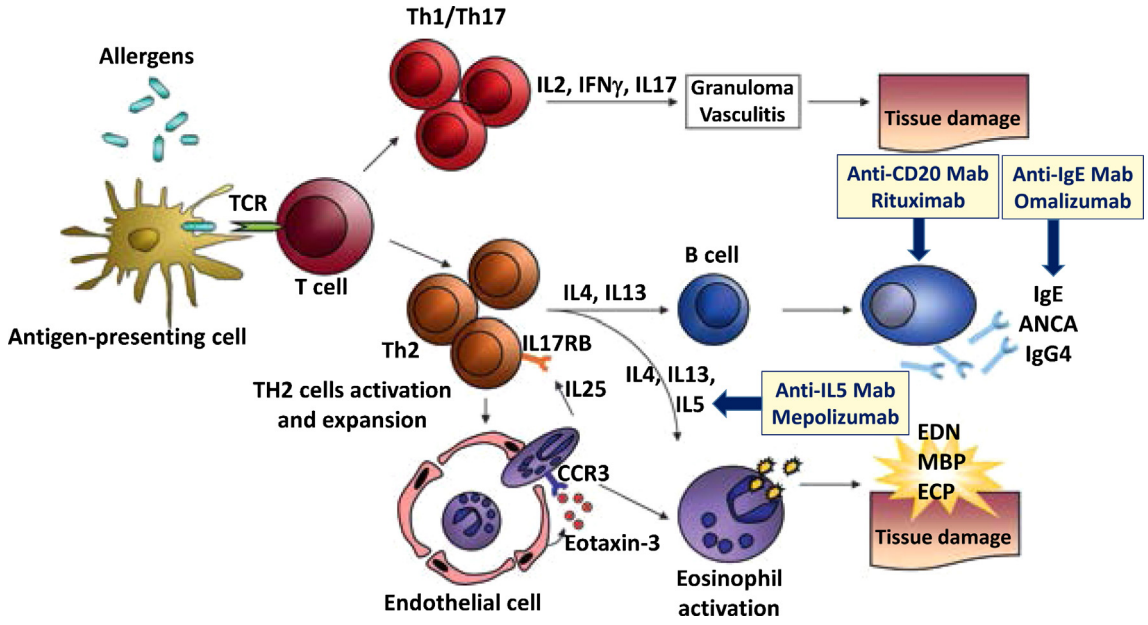

Fig. 1. Pathogenesis of eosinophilic granulomatosis with polyangiitis and therapeutic targets, adapted from [13]. Unidentified allergens induce an adaptive immune response. T-cells secrete TH1-(IFN-γ), Th17-(IL-17) and Th2-(IL-4, IL-13, IL-5) associated cytokines and activate eosinophils. The strong TH2 immune response precipitates a B-cell activation resulting in IgE, ANCA and IgG4 synthesis. Increased expression and secretion of eotaxin-3 guides eosinophils to the endothelium and tissue. In addition, peripheral mononuclear cells secrete high levels of IL-5, which promotes eosinophil activation and adhesion to endothelium. Eosinophils induce a vicious circle by secreting IL-25, which further activates T-cells. Local degranulation of activated eosinophils and release of mediators causes damage, necrosis and fibrosis to tissues and vessels. TCR: T-cell receptor; ANCA: anti-neutrophil cytoplasmic antibody; EDN: eosinophil-derived neurotoxin; MBP: major basic protein; ECP: eosinophilic cationic protein; IFN: interferon; IL-5: interleukin 5.

production is related to the inflammatory milieu conditioning B-cell maturation, and particularly to the presence of Th2 cytokines such as IL-4, IL-5 and IL-13 [17]. Furthermore, recent case reports and small retrospective series [18–24] have indicated that rituximab may also be an effective remission-induction agent in refractory or relapsing EGPA, in agreement with the results presented by Novikov et al. [10]. A review of published series of rituximab for EGPA patients is shown in Table 1. A total of 73 EGPA patients who had received rituximab, mainly for refractory or relapsing disease, have been compiled in a recent analysis [25]. Efficacy of rituximab therapy was significant in the vast majority of cases and in a wide variety of disease manifestations. The largest series to date has reported 41 EGPA patients, who received rituximab in four expert vasculitis centers, mostly for refractory or relapsing disease [24]. Patients with positive ANCA testing were significantly more likely to achieve remission at 12 months: 80% (12/15) who were ANCA-positive versus 36% (8/21) who were ANCA-negative. In contrast, Thiel et al. have reported in 9 patients, that rituximab appeared to be an efficient and safe treatment for both ANCA-positive and ANCA-negative patients [23], as also mentioned by Novikov et al. [10]. Largest prospective studies will have to clarify this issue.

In the study reported by Muhammad et al., type and rate of response did not differ between the patients treated with rituximab 375 mg/m^2 for 4 weeks or with two doses of 1 g given two weeks apart [24], as already shown in a retrospective study of patients with ANCA-associated vasculitis, of whom 5 had EGPA [26]. Apart infectious complications which may be severe in these immunocompromised patients already receiving glucocorticoids, other safety issues included infusion reactions in two patients requiring intubation due to worsening of asthma in one [24]. Severe bronchospasm has already been reported during the first 15 minutes of rituximab infusions in two EGPA patients [20]. In addition, very few patients also received rituximab as maintenance therapy in EGPA to prevent relapses. In a study, preemptive retreatment with rituximab in three patients, combined with standard maintenance immunosuppressant resulted in a sustained treatment response with a median follow-up of 3 years [23].

The mechanisms by which an anti-CD20 therapy might be efficient in EGPA remain unclear. It has been hypothesized that activated B-cells may contribute to mechanisms of tissue injury as antigen-presenting cells, regulating the development of effector T-cells by expressing costimulatory molecules, and as precursors to plasma cells, giving rise to MPO ANCA pathogenic autoantibodies. It has also been shown that rituximab mediates its beneficial actions in EGPA, at least in part, through the inhibition of T-cell IL-5 production [19]. It is interesting to note that Novikov et al. reported that all patients had improvement of their asthmatic symptoms [10].

The French Vasculitis Study Group recommended that rituximab can be prescribed to some EGPA patients whose disease is refractory to immunosuppressive therapy and responded only to high-dose corticosteroids, particularly forms characterized by predominant inflammatory vascular disease (extracapillary glomerulonephritis, alveolar hemorrhage) and the presence of anti-MPO ANCA [27].

All these promising results obtained with rituximab should be confirmed in prospective randomized controlled trials to confirm the benefit of rituximab and define the safety profile in EGPA patients. REOVAS is a randomized controlled trial, which will be implemented in EGPA patients to evaluate rituximab induction therapy as compared with standard of care. This trial designed by the French Vasculitis Study Group will start in 2015 and include 108 patients. The primary objective is to determine the efficacy of rituximab and glucocorticoids to induce a complete remission, defined as a Birmingham Vasculitis Activity Score of 0 and a prednisone dose $\leq$ 7.5 mg/day at day 180, in patients with newly-diagnosed or relapsing EGPA.

Other therapeutic immunomodulation are being evaluated in EGPA. The introduction of anti-IgE therapy for asthma inaugurated the era of biological therapies and has been shown to be useful for patients with allergic severe asthma [28,29]. EGPA patients have also been treated with omalizumab with conflicting results [30], some patients presenting vasculitis onset after omalizumab