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of

The novel approaches to the treatment of eosinophilic granulomatosis with polyangitis

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Eosinophilic granulomatosis with polyangitis (EGPA; formerly Churg–Strauss syndrome) is a systemic granulomatous vasculitis with eosinophilia in patients with a history of allergic airway diseases such as bronchial asthma [1]. Necrotizing vasculitis predominantly affects small-to-medium vessels in EGPA. EGPA is a rare disease affecting no more than 0.5 in 10,000 people globally. Pathogenesis of EGPA is unknown and presumed to be multifactorial and the disease can be triggered by exposure to allergens or drugs.

EGPA is a longstanding, life-threatening disease. Severe organ manifestations can occur in the heart, kidney and lungs. Peripheral neuropathy due to mononeuritis multiplex is also a troublesome disease condition. Five-factor score, that is, reduced renal function, proteinuria, gastrointestinal involvements (hemorrhage, infarction or pancreatitis), involvement of CNS and cardiomyopathy, can predict the prognosis of the disease [2]. Anti-neutrophilic cytoplasmic antibodies (ANCA), mainly against myeloperoxidase, are detected in approximately 40–50% of the patients; thus, EGPA is presently classified as an ANCA-associated vasculitis (AAV) [3].

Biomarkers to monitor disease activity of EGPA include blood eosinophil count and CRP. In addition, eosinophilic cationic protein and titers of myeloperoxidase-ANCA may also reflect disease activity. C-C chemokine-ligand 17 (CCL17), eotaxin-1, eotaxin-3, IL-5 and IL-25 are speculated to be involved in its pathogenesis [1]; however, their diagnostic specificity will require further study.

Glucocorticoids (GCs) remain the conventional therapy for EGPA for remission induction, however, adverse effects of GCs are frequently encountered due to their long-term use [4]. For those patients with a five-factor score of 1 or higher, cyclophosphamide (CY)-pulse therapy in association with GC is recommended since the combination therapy produces sustained remission for longer months [5]. Remission can be maintained with azathioprine or methotrexate. The target-oriented, interdisciplinary treatment can improve therapeutic outcome in EGPA [6]. However, some of the cases are resistant to conventional treatments and relapses are commonly observed. In this regard, a relapse rate of 41%, from an average of 26 months after initial treatment, has been reported [5].

Several new approaches are being taken to treat EGPA for the last several years. Among them, the most potentially effective drug is rituximab (RTX), a chimeric anti-CD20 monoclonal antibody that has been used to treat malignant lymphoma, rheumatoid arthritis and, more recently, microscopic polyangitis as well as granulomatosis with polyangitis. RTX has been proven to be efficacious for AAV in two separate studies [7,8]. It has also been shown to induce remission in AAV and to maintain it better than other agents [9]. However, until recently, its efficacy in EGPA has remained unclear. In this aspect, we successfully treated an EGPA patient with RTX who were refractory to GC, CY and intravenous gamma-

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globulin (IVIG) [10]. RTX was administered at a dose of 480 mg (375 mg/m^2) once a week for four weeks. Treatment with RTX improved cranial nerve involvement and reduced both serum eosinophilic cationic protein and CRP levels to the normal range in this case. The patient remained in remission 6 months after RTX therapy with GC reduction. Additionally, we have also identified 11 EGPA cases treated with RTX in the literature [10]. Furthermore, Tiel *et al.* [11] reported that nine EGPA patients (six ANCA-positive, three ANCA-negative) with high disease activity, who were refractory to conventional treatments, were successfully treated with RTX. A total of 3 months after RTX treatment, one patient was in complete remission and eight patients were in partial remission. CRP levels were normalized in all patients and eosinophil counts were significantly decreased even with GC tapering. Peripheral B cells measured a complete depletion in six patients. Maintenance therapy with conventional immunosuppressive drugs was followed after RTX administration. Three out of nine patients had a relapse but all of them went into remission with RTX re-treatment. No serious infection was reported in this study. RTX may target B cells functioning as antigen-presenting cells and ANCA-producing cells but its mode of action remains unclarified. RTX is therefore a promising therapy for treatment-resistant EGPA for both remission induction and maintenance therapies, although opportunistic infection including progressive multifocal leukoencephalopathy (PML) can be a problem. Tapering of GC may be possible with RTX. Further study is necessary for RTX to confirm its efficacy and safety to be a first-line drug to treat EGPA.

Targeting IL-5 can be an alternative treatment strategy in EGPA. Mepolizumab is a fully humanized IgG monoclonal antibody against IL-5. IL-5 is a key cytokine that regulates the growth, activation and survival of eosinophils and its serum concentration is reported to be increased in EGPA. Neutralization of IL-5 with mepolizumab was efficacious in an uncontrolled trial [12]. Eight out of nine patients reached a remission at week 32 by mepolizumab with GC dosage of less than 7.5 mg/day. No relapse was observed and no serious adverse effect was seen with mepolizumab therapy. Orphan designation of mepolizumab for the treatment of EGPA was granted to the pharmaceutical company by the European Commission last year. A double-blind, randomized, placebo-controlled trial to investigate the efficacy and safety of mepolizumab in relapsing or refractory EGPA patients has just started in early 2014 in the USA (NCT02020889).

Omalizumab, a humanized anti-IgE monoclonal antibody, inhibits IgE binding to IgE receptors and binds free IgE in serum. It has been approved for severe allergic asthma patients with high serum IgE in many countries. A remission was induced with omalizumab in a pediatric EGPA patient who was resistant to GC, CY, IVIG, RTX and mycophenolate mofetil [13]. Omalizumab was given at 300 mg subcutaneously every two weeks according to the package insert. Both respiratory and gastrointestinal symptoms were completely controlled with omalizumab, and GC was tapered to 5 mg/day in this case. On the contrary, Wechsler *et al.* [14] have identified a development of an EGPA-like condition in patients with asthma treated by omalizumab. This demonstrates the temporal correlation between leukotriene-receptor antagonists and EGPA [15]. It might be possible that omalizumab itself triggers EGPA or unmasks EGPA due to the tapering of GC. Consequently, one may have to be cautious to apply this biologic for the treatment of EGPA.

IVIG combined with or without plasmapheresis has been reported to be effective in EGPA. Tsurikisawa *et al.* [16] have reported that IVIG showed significant improvement in muscle weakness, dysesthesia and cardiac output in 22 EGPA patients refractory to conventional treatment compared with 24 patients who did not receive IVIG. In patients treated with IVIG, a significant increase of regulatory T cells was also observed. IVIG has therefore been approved for GC-resistant peripheral neuropathy caused by EGPA in Japan. IVIG may also be an alternative to immunosuppressants in pregnant patients. However, it is not proved whether IVIG monotherapy can induce remission in EGPA. Furthermore, availability of IVIG, cost and safety must be cautiously evaluated.

IFN-α can inhibit eosinophil degranulation and reverse Th2-mediated immune response. IFNα (3 million units, three times a week) was administered in a prospective open-label trial to seven EGPA patients refractory to conventional treatment [17]. All patients achieved remission but frequent relapses were observed after cessation of IFNα. Serious side effects, such as depression and cardiac failure, can be encountered and limit its wider application in EGPA. Since then, no further clinical trial has been undertaken.

Other drugs, such as tyrosine-kinase inhibitors, mycophenolate mofetil and TNF antagonists, may be possible candidates for a novel approach, but use of these drugs for EGPA remain as anecdotal reports, that is, none of them have been evaluated in a prospective controlled trial.

In conclusion, several promising drugs that may be possible to replace GC to induce and maintain remission are emerging in the treatment of EGPA. Better understanding of the disease pathogenesis will allow us to perform more selective targeting therapies. Fur-

thermore, randomized, controlled trials in a multicenter design to prove their efficacy and safety must be carried out.

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• of interest; •• of considerable interest

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