

**Efficacy of Benralizumab and Clinical Course of IgG4 on Eosinophilic
Granulomatosis with Polyangiitis**

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0648

Keywords: EGPA. Benralizumab. Anti-IL-5 receptor antibody. IgG4.
MPO-ANCA.

Palabras clave: Granulomatosis eosinofílica con poliangiitis (GEPA).
Anticuerpo antirreceptor de IL-5. IgG4. Anticuerpos MPO-ANCA.

Eosinophilic granulomatosis with polyangiitis (EGPA) clinically presents as a systemic eosinophilic disease with asthma and eosinophilia [1], causing eosinophilic necrotizing granulomatous inflammation damaging the respiratory organs and necrotizing angiitis affecting the small blood vessels. Systemic glucocorticoids are generally used as the first-line treatment to attain remission in EPGA; however, they cannot be used for long-term therapy due to their potential adverse effects. Recent studies have shown that mepolizumab, a biologic interleukin (IL)-5 antibody agent, suppresses EGPA recurrence [2]; however, half of the patients in these studies did not achieve remission even when mepolizumab co-administered with glucocorticoids, and thus, it is crucial to discover more effective drugs. Benralizumab is a humanized monoclonal antibody against the α -chain of the IL-5 receptor, which suppresses eosinophil activation by directly and specifically binding to and inhibiting the IL-5 receptor [3]. Several studies have demonstrated the efficacy of benralizumab; a case report showed that benralizumab administration reduced the levels of

myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) [4], and another case report showed an effect on refractory EGPA [5]. However, the long-term prognosis following benralizumab therapy remain unclear. Moreover, previous studies have shown that serum immunoglobulin (Ig) G4 in EGPA is correlated with Birmingham vasculitis activity score (BVAS) and the number of damaged organs and is elevated in eosinophilia and EGPA patients [6]. However, the effect of biologic agents on serum IgG4 levels has not yet been evaluated. We present a patient with steroid-refractory MPO-ANCA positive EGPA successfully treated with benralizumab who went on to disease remission, as assessed by clinical and laboratory tests including significantly decreased serum IgG4 levels. The prednisolone dose was reduced to 4 mg/day over two years while monitoring the serum IgG4 levels.

Three years ago, the 38-year-old man was diagnosed with asthma and allergic rhinitis at another hospital. His asthma was treated with 500 µg inhaled fluticasone propionate/50 µg salmeterol twice daily, 10 mg/day montelukast sodium, and 400 mg/day theophylline. Three years after starting the asthma treatment, the patient was admitted to the hospital because of dyspnea, malaise, rash on both legs, and upper and lower extremity numbness. According to the American College of Rheumatology criteria, he was diagnosed with EGPA complicated by asthma, eosinophilia ($\geq 10\%$ white blood cells), polyneuropathy, and sinusitis, as well as eosinophil infiltration by tissue biopsy of ulcers from the lower extremities. MPO-ANCA was also positive. Prednisolone (60 mg/day)

was started as an initial treatment, and its effects were assessed by BVAS, eosinophil count, C-reactive protein (CRP), MPO-ANCA, asthma control test (ACT), and pulmonary function tests. Further, serum IgG4 levels were also measured. As the eosinophil count and CRP improved, the dose was reduced to 30 mg/day on the 49th day after the start of prednisolone administration. However, there were no further improvements in the eosinophil count and symptoms; thus, reduction in prednisolone dosage was difficult. Additional treatment with an immunosuppressant was declined by the patient because he and his family had a strong desire for childbearing. Considering the poor control of asthma, administration of 30 mg benralizumab was started for both EGPA and asthma. After four weeks of benralizumab administration, the number of eosinophils improved from 1330 to 0/ μ L, MPO-ANCA from 48.5 to 0.9 IU/mL, and BVAS from 16 to 7. Moreover, IgG4 level at the time of admission was 406 mg/dL, which reduced to 311 mg/dL after systemic glucocorticoid administration, however, significantly improved to 100 mg/dL after four weeks of benralizumab treatment. ACT scores improved from 18 points before treatment to 25 points at four weeks post-treatment. Pulmonary function tests showed a significant increase of 740 mL in forced expiratory volume in one second at four weeks compared with that at baseline (Figure 1). The dose of prednisolone was gradually tapered to 4 mg/day, which is one criterion for the remission of EGPA in clinical trials in combination with benralizumab [2]. Currently, by combination treatment with prednisolone and benralizumab, exacerbation of EGPA has not been observed for 104 weeks.

IgG4 is mainly generated by chronic antigen stimulation [6]. Because the Th2 cytokines, IL-4, IL-5, and IL-13, promote class switching to IgG4,

suppression of IL-5 may prevent IgG4 production and contribute to the control of EGPA. In addition, rituximab, a therapeutic agent for EGPA, has been reported to reduce humoral immunity [7] and it is considered important for the suppression of humoral immunity and IgG class switching to improve EGPA. Furthermore, although the clinical expression for direct and easily evaluation of vascular inflammation in EGPA remains unclear, comparing to serum MPO-ANCA levels which were undetectable after 4 weeks of benralizumab treatment, serum IgG4 levels might be promising for evaluating vascular inflammation during biological treatments. Regarding the increase in IgG4 from 8 to 32 weeks, we think that the BVAS level is also increasing, and there may have been a slight exacerbation that does not appear in eosinophil count, CRP, and MPO-ANCA. We also think that the IgG4 levels may have reflected those changes. BVAS, a measure for systemic organ dysfunction, tended to decrease after benralizumab administration. In particular, the mononeuritis multiplex that was initially recognized was also improved by benralizumab. Mononeuritis multiplex in vasculitis is caused mainly due to ischemia of the peripheral nerves and accompanying axon damage. However, exacerbation of mononeuritis multiplex was not observed after steroid tapering, suggesting that a disorder due to eosinophil infiltration was also involved. In this patient, the peripheral blood eosinophil count was nearly zero at four weeks after benralizumab administration, agreeing with previous asthma clinical trials and showing a marked early decrease [8-9]. Fucose has been removed from the Fc region of benralizumab allowing natural killer cells to recognize benralizumab bound to eosinophils, stimulating antibody-dependent cell-mediated cytotoxicity, facilitating apoptosis of eosinophils[10]. This action may have contributed to

reducing the dose of prednisolone without obvious exacerbation in this patient.

In conclusion, we show the efficacy of benralizumab on EGPA and a significant improvement in IgG4 levels. To the best of our knowledge, this is the first patient to show reduction in IgG4 upon administration of biologics. The administration of benralizumab for MPO-ANCA-positive EGPA enabled the tapering of prednisolone to 4 mg/day. The effect persisted for 104 weeks. Hence, benralizumab, effectively removing eosinophils from tissues, may help in controlling EGPA. Moreover, quantification of IgG4 may be a clinical expression for evaluating vascular inflammation in EGPA and/or monitoring the effects of benralizumab treatment.

Conflicts of interest

No potential conflict of interest was disclosed.

Financial Disclosure

None.

Non-financial Disclosure

None.

Funding

None.

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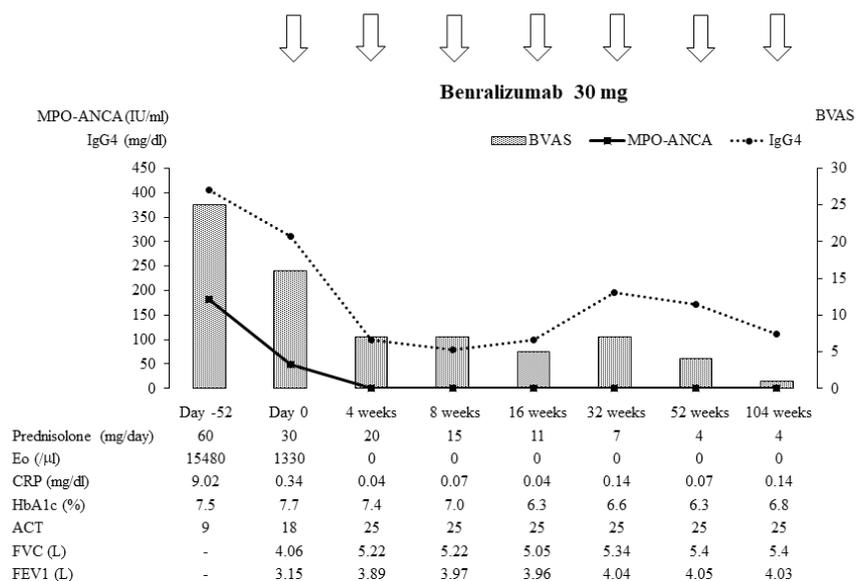
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Figures

Figure 1. Clinical course of a patient with MPO-ANCA-positive EGPA treated with benralizumab for 104 weeks.

Figure 1



Day-52 is the first consultation day in our hospital. Day 0 is the date of first administration of benralizumab.

ACT: asthma control test. BVAS: Birmingham Vasculitis Activity Score. CRP: C-reactive protein. Eo: eosinophil count. FEV₁: forced expiratory volume in one second. FVC: forced vital capacity. Ig: immunoglobulin. MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody.