Efficacy of Benralizumab and Clinical Course of IgG4 in Eosinophilic Granulomatosis With Polyangiitis

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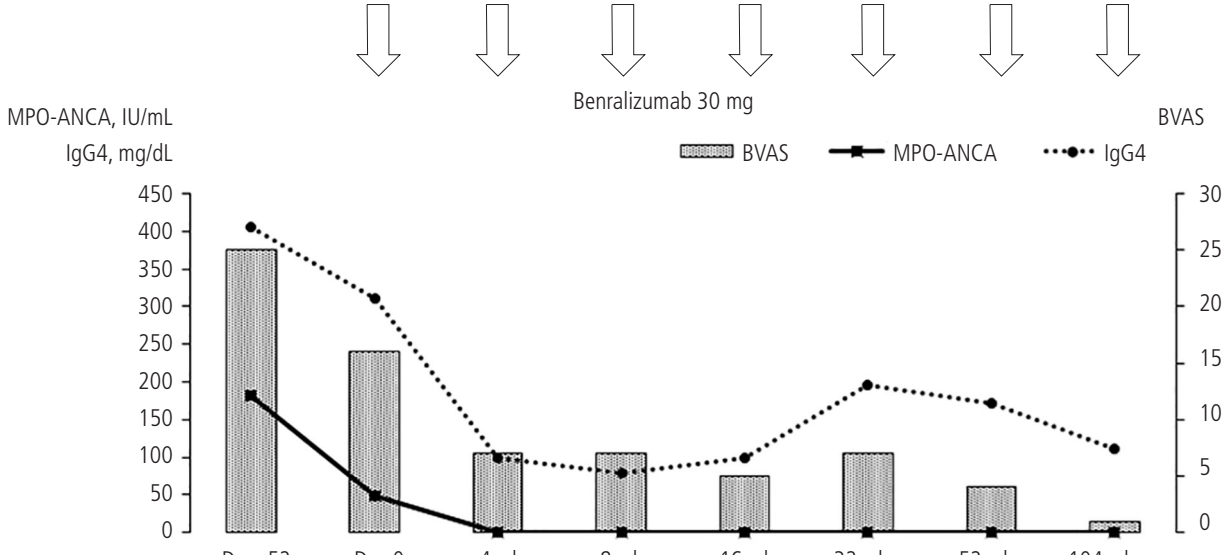
Palabras clave: Granulomatosis eosinofílica con poliangitis (GEPA). Benralizumab. Anticuerpo antirreceptor de IL-5. IgG4. Anticuerpos MPO-ANCA.

Eosinophilic granulomatosis with polyangiitis (EGPA) presents clinically as a systemic eosinophilic disease with asthma and eosinophilia [1]. It causes eosinophilic necrotizing granulomatous inflammation, which damages the respiratory organs, and necrotizing angiitis, which affects the small blood vessels. Systemic corticosteroids are generally used as the first-line treatment to attain remission in EGPA, although they cannot be used for long-term therapy owing to their potential adverse effects. Mepolizumab, a biologic interleukin (IL) 5 antibody, has been shown to suppress recurrence of EGPA [2]; however, half of the patients studied did not achieve remission, even when mepolizumab was coadministered with corticosteroids. Therefore, it is crucial to discover more effective drugs. Benralizumab is a humanized monoclonal antibody that acts against the IL-5 receptor α chain, 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; one case report showed that benralizumab reduced levels of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) [4], and another showed an effect on refractory EGPA [5]. However, long-term prognosis following therapy with benralizumab remains unclear. Previous studies have shown that serum immunoglobulin (Ig) G4 in EGPA is correlated with the Birmingham Vasculitis Activity Score (BVAS) and the number of damaged organs and is elevated in patients with eosinophilia and EGPA [6]. However, the effect of biologic agents on serum IgG4 levels has not yet been evaluated. We present the case of a patient with corticosteroid-refractory, MPO-ANCA–positive EGPA successfully treated with benralizumab. The patient achieved remission, as shown by the results of clinical and laboratory tests, including significantly decreased serum IgG4 levels. The prednisolone dose was reduced to 4 mg/d over 2 years while serum IgG4 levels were monitored.

Three years ago, a 38-year-old man was diagnosed with asthma and allergic rhinitis at another hospital. His asthma was treated with inhaled fluticasone propionate 500µg/

salmeterol 50 µg twice daily, montelukast sodium 10 mg/d, and theophylline 400 mg/d. Three years after starting asthma treatment, the patient was admitted to hospital because of dyspnea, malaise, rash on both legs, and numbness of the upper and lower extremities. According to the American College of Rheumatology criteria, he was diagnosed with EGPA complicated by asthma, eosinophilia (≥10% white blood cells), polyneuropathy, and sinusitis, as well as eosinophilic infiltration, which was demonstrated by tissue biopsy of ulcers from the lower extremities. The MPO-ANCA titer was also positive. He was initially treated with prednisolone (60 mg/d), whose effects were assessed based on the BVAS, eosinophil count, C-reactive protein (CRP), MPO-ANCA titer, Asthma Control Test (ACT) score, and pulmonary function tests. Serum IgG4 levels were also measured. As the eosinophil count and CRP improved, the dose was reduced to 30 mg/d on the 49th day after initiation. However, given that there were no further improvements in the eosinophil count or symptoms, the prednisolone dosage could not be reduced. Additional treatment with an immunosuppressant was declined by the patient because he and his partner had a strong desire to start a family. Considering the poor control of asthma, benralizumab 30 mg was started for both EGPA and asthma. After 4 weeks of therapy with benralizumab, values improved for eosinophils from 1330 to 0/µL, MPO-ANCA from 48.5 to 0.9 IU/mL, and the BVAS from 16 to 7. Moreover, the IgG4 level, which was 406 mg/dL at admission, decreased to 311 mg/dL after treatment with systemic corticosteroids, before improving significantly, falling to 100 mg/dL after 4 weeks of treatment with benralizumab. The ACT score improved from 18 points before treatment to 25 points at 4 weeks after treatment. Pulmonary function tests showed a significant increase of 740 mL in forced expiratory volume in 1 second at 4 weeks compared with baseline (Figure). The dose of prednisolone was gradually tapered to 4 mg/d, which, in combination with benralizumab, is a criterion for remission of EGPA in clinical trials [2]. Since initiation of combination treatment with prednisolone and benralizumab, no exacerbations of EGPA have been observed (104 weeks).

IgG4 is mainly generated by chronic antigen stimulation [6]. Because the type 2 helper T 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, which is used to treat EGPA, has been reported to reduce humoral immunity [7] and is considered important for the suppression of humoral immunity and for the IgG class switching necessary to improve EGPA. Furthermore, although the role of clinical expression of serum IgG4 in direct and easy evaluation of vascular inflammation in EGPA remains unclear, compared with serum MPO-ANCA levels, which were undetectable after 4 weeks of benralizumab treatment, it could prove to be promising for evaluation of



	Day -52	Day 0	4 wk	8 wk	16 wk	32 wk	52 wk	104 wk
Prednisolone, mg/d	60	30	20	15	11	7	4	4
Eo, µL	15480	1330	0	0	0	0	0	0
CRP, mg/dL	9.02	0.34	0.04	0.07	0.04	0.14	0.07	0.14
HbA1c, %	7.5	7.7	7.4	7.0	6.3	6.6	6.3	6.8
ACT	9	18	25	25	25	25	25	25
FVC, L	-	4.06	5.22	5.22	5.05	5.34	5.4	5.4
FEV_1, L	-	3.15	3.89	3.97	3.96	4.04	4.05	4.03

Figure. Clinical course of a patient with MPO-ANCA–positive EGPA treated with benralizumab for 104 weeks. His first visit to our hospital was on day 52. Day 0 is the date of his first dose of benralizumab. ACT indicates asthma control test; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; Eo, eosinophil count; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; Ig, immunoglobulin. MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody.

vascular inflammation during biological treatments. The increase in IgG4 from 8 to 32 weeks was accompanied by an increase in the BVAS and a slight exacerbation that is not reflected in the eosinophil, CRP, or MPO-ANCA values. We also think that the IgG4 levels may be associated with those changes. BVAS, which is a measure for systemic organ dysfunction, tended to decrease after administration of benralizumab. In particular, the mononeuritis multiplex that was initially recognized also improved with benralizumab. Mononeuritis multiplex in vasculitis results mainly from ischemia of the peripheral nerves and accompanying axonal damage. However, exacerbation of mononeuritis multiplex was not observed after tapering of corticosteroids, suggesting that a disorder due to eosinophil infiltration was also involved. In the present case, the peripheral blood eosinophil count was nearly zero at 4 weeks after administration of benralizumab, agreeing with findings from previous clinical trials in asthma that show a marked early decrease [8-9]. Removing fucose from the Fc region of benralizumab enables natural killer cells to recognize benralizumab bound to eosinophils, thus stimulating antibody-dependent cell-mediated cytotoxicity and facilitating apoptosis of eosinophils [10]. This action may have helped to reduce the dose of prednisolone without obvious exacerbation in the case we report.

In conclusion, we show the efficacy of benralizumab in EGPA and a significant improvement in IgG4 levels. To the best of our knowledge, this is the first patient in whom IgG4 decreased upon administration of biologics. The administration of benralizumab for MPO-ANCA–positive EGPA enabled prednisolone to be tapered to 4 mg/d. The effect persisted for 104 weeks. Hence, benralizumab effectively removes eosinophils from tissues and may help to control EGPA. Moreover, quantification of IgG4 may act as a clinical marker of vascular inflammation in EGPA and could be used to monitor the effects of benralizumab.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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