Case Report

Benralizumab monotherapy was insufficient to induce remission in patients with active eosinophilic granulomatosis with polyangiitis

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ARTICLE INFO

Keywords:
Benralizumab
Eosinophilic granulomatosis with polyangiitis
Corticosteroid

ABSTRACT

Eosinophils play an important pathogenetic role in the development of eosinophilic granulomatosis with polyangiitis (EGPA). EGPA has long been treated with systemic corticosteroids and immunosuppressive agents. However, in recent years, biologic agents targeting eosinophils (anti-IL-5 antibody; mepolizumab) have also been used. Evidence regarding the effectiveness of using benralizumab, anti-IL-5 receptor α monoclonal antibody that depletes eosinophils via antibody-dependent cell-mediated cytotoxicity, has been growing. Benralizumab is used as a steroid-sparing treatment option for EGPA. Clinical studies have evaluated the effects of using mepolizumab or benralizumab in combination with steroids for the treatment of EGPA. However, to date, there have been no reports of using biologics alone. Herein, we describe the case of a patient with active EGPA refractory to benralizumab monotherapy. The patient achieved significant improvement in symptoms after administration of corticosteroids during hospitalization. Benralizumab monotherapy might not be considered a therapeutic option for patients with active EGPA in whom corticosteroids are initially indicated.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by excessive eosinophil accumulation in the peripheral blood and impacted tissue, developing into granulomatous vasculitic organ damage. EGPA typically develops into the following three phases: (i) onset of asthma associated with rhinosinusitis; (ii) tissue eosinophilia; and (iii) extrapulmonary eosinophilic involvement in vasculitis [1,2]. Although corticosteroids are the mainstay of EGPA treatment that can dramatically improve prognosis, most patients remain dependent on oral corticosteroid (OCS) therapy, and commonly experience [1,2]. Standard induction regimen for EGPA comprises high-dose corticosteroids with or without immunosuppressive agents. Mepolizumab (anti-interleukin(IL)-5 antibody) is the only treatment of EGPA that has been shown to be safe and effective in reducing corticosteroid dosage and disease recurrence [3]. Chica-Guzmán et al. reported that benralizumab as treatment of EGPA led to a sustained clinical improvement, along with OCS withdrawal [4]. Benralizumab, an anti-IL-5 receptor α monoclonal antibody that depletes eosinophils via antibody-dependent cell-mediated cytotoxicity, has been indicated for treatment of eosinophilic asthma [5]. A growing number of reports have demonstrated the clinical efficacy of benralizumab in patients with EGPA [4,6,7]. We describe a case of highly active EGPA that failed to achieve remission after benralizumab monotherapy.

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; IL, interleukin; ACR/EULAR, American College Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR); CT, computed tomography.
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https://doi.org/10.1016/j.rmcr.2022.101763
Received 21 June 2022; Received in revised form 11 October 2022; Accepted 24 October 2022
Available online 30 October 2022
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2. Case presentation

A 58-year-old man was admitted after an episode of purpuric skin eruption with blisters and ulcers, pain, and paresthesia of bilateral lower limbs. He had a 12-year history of asthma and was diagnosed with eosinophilic chronic rhinosinusitis (ECRS) at the age of 40. Four weeks prior to admission, the patient was diagnosed with eosinophilic pneumonia due to increased blood eosinophil counts (13,680/μL) and ground-glass shadows on chest radiograph and computed tomography (CT) (Fig. 1). His serum total immunoglobulin (Ig)E was 2,080 IU/mL. Aspergillus serology blood test revealed negative results. The results of chemiluminescent enzyme immunoassay testing showed a slight increase in the levels of myeloperoxidase anti—neutrophil cytoplasmic antibody (MPO-ANCA) (10.8 IU/ml; normal reference: < 3.5 U/ml). At age of 47, his left lung was removed due to bronchial tuberculosis. Therefore, he initially refused to take steroids, fearing tuberculosis relapse. The patient was treated for eosinophilic pneumonia with benralizumab (30mg administered subcutaneously) alone instead of corticosteroids. After treatment with benralizumab, the eosinophil count decreased from 13,680/μL to 2,450/μL at one week, to 110/μL at two weeks, and then increased again to 760/μL at three weeks. One week after benralizumab administration, pain appeared in the lower extremities, followed by numbness in the lower extremities at two weeks later. Moreover, three weeks after benralizumab administration, skin rash with ulceration occurred, resulting in hospitalization. The MPO-ANCA level had increased to 130 IU/ml. A skin biopsy of lower limb purpura revealed fibrinoid necrotic vasculitis of the superficial blood vessels, along with nuclear dust and perivascular eosinophilic dermatitis with neutrophil and granulomatous inflammation (Fig. 2). Since all six of the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria were met, the patient was diagnosed with EGPA [8]. These criteria include: asthma, chronic rhinosinusitis, eosinophilia >10%, transient pulmonary opacities, polyneuropathy and extravascular eosinophils on histology. Prednisone treatment (60 mg daily) was initiated. The patient’s symptoms rapidly improved. In addition, the prednisone dosage was gradually tapered. Written informed consent was obtained from the patient for the publication of this report.

3. Discussion

Standard induction therapy for EGPA is high-dose corticosteroids with or without immunosuppressive agents [2]. Mepolizumab in combination with corticosteroids for EGPA has been reported to be effective in induction of remission [3]. It is unclear whether EGPA can be controlled by suppressing eosinophils though inhibition of IL-5. In the present case, the patient was diagnosed with eosinophilic pneumonia based on increased eosinophil count and ground-glass shadows on chest CT. Thus, we initiated treatment with benralizumab. Subsequently, the patient was diagnosed with EGPA, according to the ACR/EURA criteria, and treated with prednisone. Benralizumab is known to deplete eosinophils from peripheral blood and tissues immediately after administration. However, in this case, eosinophils were reduced to some extent without depletion from the peripheral blood. Colantuono et al. reported a case of EGPA in which benralizumab added to steroids resulted in 0/μL of eosinophils and improvement in asthma control, peripheral neu-

![Fig. 1.](image-url) (a) Chest radiograph showed an infiltrative shadow in the right upper lung field. (b) Chest CT showed multiple ground-glass shadows on the outer side of the right lung.
rapeathy, and cardiomyopathy. In their case, although eosinophils also increased again during benralizumab treatment, they remained below the upper normal limit (<500/μL) [9]. Caminati reported a case of EGPA during treatment of severe asthma with zero eosinophils after treatment with benralizumab, in which an increase in peripheral blood eosinophil count was observed at EGPA onset [10]. Th2 responses are prominent, with the up-regulation of IL-4, IL-13, and IL-5. However, Th1 and Th17 responses are not negligible. Regulatory T cells are diminished during active EGPA. B cells and humoral response have been reported as further contributors to EGPA pathogenesis [11]. Eosinophils are also well known to regulate the function of other leukocytes [12]. Therefore, controlling eosinophils may also assist in regulating other leukocytes. The inability to deplete eosinophils even with benralizumab, as in this case, suggests that eosinophil activity in EGPA might be considerably stronger than in severe eosinophilic asthma.

It is unclear whether eosinophils were involved in the pathogenesis of vasculitis in patients with EGPA. Bormioli et al. reported a patient with EGPA who could not continue immunosuppressive drugs due to liver dysfunction (methotrexate and azathioprine) and their ineffectiveness (cyclosporine and anti-TNFα mAb; infliximab). The patient was treated with mepolizumab, leading to reduction in OCS dose but worsening asthma. In that previously described patient, a transbronchial biopsy showed capillaritis with eosinophils infiltration (positive expression of IL-5Rα) around the blood vessels. However, when that patient was switched from mepolizumab to benralizumab, asthma improved and vasculitis disappeared [13]. There have been also several case reports of reduced ANCA levels after benralizumab treatment [7,14,15]. In all these cases in which vasculitis in EGPA improved with benralizumab treatment, OCS was concomitantly used. Lim et al. reported a case of exacerbation of purpuric rash with ulceration; arthralgia and upper respiratory symptoms; increases in eosinophils from 0 to 4,600/μL; and ANCA positivity when OCS was reduced to <10 mg/day during benralizumab treatment. Furthermore, in this case, EGPA flared up when peripheral eosinophil counts were undetectable one week prior to admission, subsequently, increased blood eosinophils were detected. Benralizumab could treat the eosinophil-driven aspect of the disease without affecting vasculitis, thereby allowing EGPA to develop despite eosinophil depletion. Kolios et al. described that benralizumab was effective as initiation and maintenance therapy for the cardiac and central nervous systems in combination with concomitant antibiotic treatment of sepsis. Subsequently, multiple cerebral infarctions occurred and steroids were administered, even though the peripheral blood eosinophils were 0/μL. Steroids were subsequently discontinued, and the patient was treated with benralizumab alone [16].

Our patient was treated with benralizumab alone in the late tissue eosinophilia phase before the vasculitis phase. However, this treatment failed to completely deplete the eosinophils; thus, it did not halt disease progression. Further studies are needed to evaluate the complex relationship of EGPA with anti-IL-5 therapy, which may be of value in the treatment of eosinophil-driven diseases.

4. Conclusion

Crosstalk between eosinophils and other immune cells has been reported. Therefore elucidating how vasculitis develops when eosinophilic inflammation is completely controlled in patients with EGPA is required. Benralizumab (30mg) alone does not seem to
suppress eosinophilic inflammation in active patients with EGPA. It remains to be clarified whether the increased dose of benralizuab alone or in combination with steroids could adequately control eosinophilic inflammation in patients with active EGPA.

Ethics approval and consent to participate

The presented data are part of our clinical work, and there are no ethical conflicts.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Consent for publication

Written consent for publication of this report was obtained from the patient, and a copy of the consent form can be shared, if required.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

We thank Dr. Jun Akome for the skin biopsy and management. We thank Kyoko Uekawa, Shoko Tachibana and Marina Miyazaki for assisting in the preparation of this manuscript.

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