



Case report

Rapid and sustained effects of a single dose of benralizumab on chronic eosinophilic pneumonia

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ABSTRACT

Chronic eosinophilic pneumonia (CEP) is an eosinophilic inflammatory disease of unknown etiology, and oral corticosteroid (OCS) is commonly used for its treatment. Approximately half of CEP cases relapse secondary to reduction or termination of OCS. A 43-year-old woman visited our hospital because of a chronic cough and abnormal chest X-ray findings. She was diagnosed with CEP because of marked eosinophilia, as well as eosinophilic infiltrates in cryobiopsy samples. After initiation of OCS treatment, her symptoms disappeared with a decrease in peripheral blood eosinophil counts and the amelioration of abnormal infiltrative shadows on chest X-ray. However, symptoms reappeared after OCS termination, including a recurrence of eosinophilia and appearance of fresh abnormal shadows on chest X-ray. Because she refused readministration of OCS because of side effects such as appetite enhancement and moon face in last treatment course, we administered her a single dose of benralizumab. Her symptoms and peripheral eosinophil counts were markedly ameliorated 1 week after benralizumab administration. The marked amelioration in abnormal shadows on chest X-ray were maintained 2 weeks after benralizumab administration. She had no relapse of CEP for almost 6 months after benralizumab administration. Our experience with this case suggests that a single dose of benralizumab may be a treatment option for relapsed CEP cases or those with side effects of long-term OCS therapy.

1. Introduction

Chronic eosinophilic pneumonia (CEP) is an inflammatory disease characterized by the appearance of pulmonary eosinophilic infiltrates [1] that permeate the lungs, causing cough, fever, and dyspnea [2]. Oral corticosteroid (OCS) is commonly used to treat CEP, and patients usually show a good response to the treatment [3]. However, CEP recurs during steroid dose reduction or termination in approximately 50% cases [3]. Many such cases require long-term OCS administration, but the side effects of long-term OCS administration, such as osteoporosis, moon face, and increase of infections may become problematic in them [4]. Therefore, new treatments are needed for cases in which use of systemic OCS is challenging or in which there is treatment resistance.

Here we report a case of relapsed CEP in which a single dose of benralizumab achieved successful remission.

2. Case report

A 43-year-old woman visited our hospital because of a chronic cough and abnormal chest X-ray findings. She had a history of smoking 10 cigarettes a day, but did not have a history of lung disease (including bronchial asthma). Laboratory data showed an elevated white blood cell count (17,080/ μ L) with marked eosinophilia (7420/ μ L), without elevation of proteinase 3 antineutrophil cytoplasmic antibody (PR-3 ANCA), myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA), or Krebs von den Lungen-6 (KL-6). The C-reactive protein level was slightly elevated (3.04 mg/dL) and chest X-ray showed infiltrative shadows in the upper lung fields bilaterally (Fig. 1A). Chest computed tomography (CT) showed consolidation and ground-glass opacity (GGO) in bilateral upper lobes (Fig. 1B). Fiberoptic bronchoscopy did not reveal any abnormal findings in the bronchial lumen. The pathological

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CEP, chronic eosinophilic pneumonia; CT, computed tomography; GGO, ground-glass opacity; IL-5, interleukin 5; OCS, oral corticosteroid.

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examination of bronchial cryobiopsy specimens obtained from the right B3a (Fig. 1C) showed high levels of eosinophil infiltration in the alveolar space (Fig. 1D). She was diagnosed with CEP on the basis of eosinophilic infiltration in cryobiopsy specimens, along with marked peripheral eosinophilia, infiltrative shadows on chest X-ray and CT, and negative findings for other causes of cough and pulmonary infiltrates. Treatment with prednisolone 30 mg/d (0.5 mg/kg/d) was started and the dose was gradually tapered. She responded to the treatment and her symptoms disappeared with a decrease in peripheral blood eosinophil counts (Fig. 2), along with an amelioration of abnormal shadows on chest X-ray. She had quit smoking after steroid treatment. However, her symptoms worsened after prednisolone termination, and her peripheral eosinophil counts rebounded (Fig. 2). Fresh abnormal infiltrative shadows appeared in the right upper lung field (Fig. 3A). She was subsequently diagnosed with a CEP relapse and was offered prednisolone readministration; however, she refused same because of the side effects such as appetite enhancement and moon face of the first course of OCP. A single dose of benralizumab 30 mg was subsequently administered as an alternative. One week after administration of benralizumab, her symptoms almost disappeared completely and the peripheral eosinophil count became zero. Abnormal infiltrates in the right upper lung field also ameliorated on chest X-ray (Fig. 3B). Abnormal infiltrates in the right upper lung field were markedly ameliorated on chest X-ray 2 weeks after benralizumab administration (Fig. 3C). Marked ameliorations in the abnormal findings on chest X-ray and CT were sustained even 1 month afterward (Fig. 3D and E). At the time of drafting of the case report almost 6 months after benralizumab administration, the patient has not shown CEP relapse and remains asymptomatic (Fig. 3F).

3. Discussion

To our knowledge, this is the first case report on the rapid and sustained effects of a single dose of benralizumab on CEP. CEP symptoms, blood eosinophil counts, and abnormal chest X-ray findings were unexpectedly ameliorated with just a single dose of benralizumab. Moreover, these effects lasted until our last follow-up, which was approximately 6 months after benralizumab administration.

Benralizumab is a humanized fucosylated monoclonal antibody that targets the interleukin 5 (IL-5) α receptor [5]. In contrast to anti-IL-5

monoclonal antibodies, benralizumab exerts its effect by inducing a direct, rapid, and nearly complete depletion of peripheral blood eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). This is an apoptotic process of eosinophil elimination involving natural killer cells (Pharm 2016). We have previously reported a case of lung cancer with severe eosinophilic asthma [6] in which benralizumab showed a rapid clinical effect as well as marked decrease in eosinophils in the pathological examination of lung tissue specimens. In the current case, it is considered that the symptoms and abnormal chest X-ray findings were ameliorated by the rapid removal of eosinophils from the bronchi and lung tissue after benralizumab administration. The ADCC-mediated eosinophil removal effect caused by benralizumab must have also contributed to the amelioration of CEP symptoms.

Previous studies have reported a reduction in the peripheral blood eosinophil levels after single dose of benralizumab; the effect lasted for at least 8 weeks at doses of 0.03–0.1 mg/kg and for at least 12 weeks at doses of 0.3–3 mg/kg [7,8]. There is also a report that blood eosinophil counts were approximately zero for approximately 5 months following a single dose of benralizumab [9]. These long-term effects of benralizumab might be related to the effectiveness in our case.

CEP is an inflammatory disease characterized by eosinophilic infiltration in the lung of unknown etiology. Therefore, the cause of CEP is a very difficult problem. Resent several studies reported that chronic accumulation of eosinophils in the alveolar space induced by IL-5 was suggested to play a major role in the development of CEP. The pathogenesis of CEP remains unknown, however, it might be discussed that IL-5-mediated eosinophil recruitment in the alveoli plays an important role in the CEP [10,11].

In conclusion, we described the rapid and sustained reduction of eosinophils in the lung and airway tissues after a single dose of benralizumab along with the amelioration of clinical findings in a patient with relapsed CEP. It is not known if the effects will last for over 6 months. Our experience suggests that a single dose of benralizumab may be a treatment option in cases of CEP relapse or in cases where serious adverse effects of OCS. Further prospective studies are needed to evaluate the effectiveness of benralizumab for CEP.

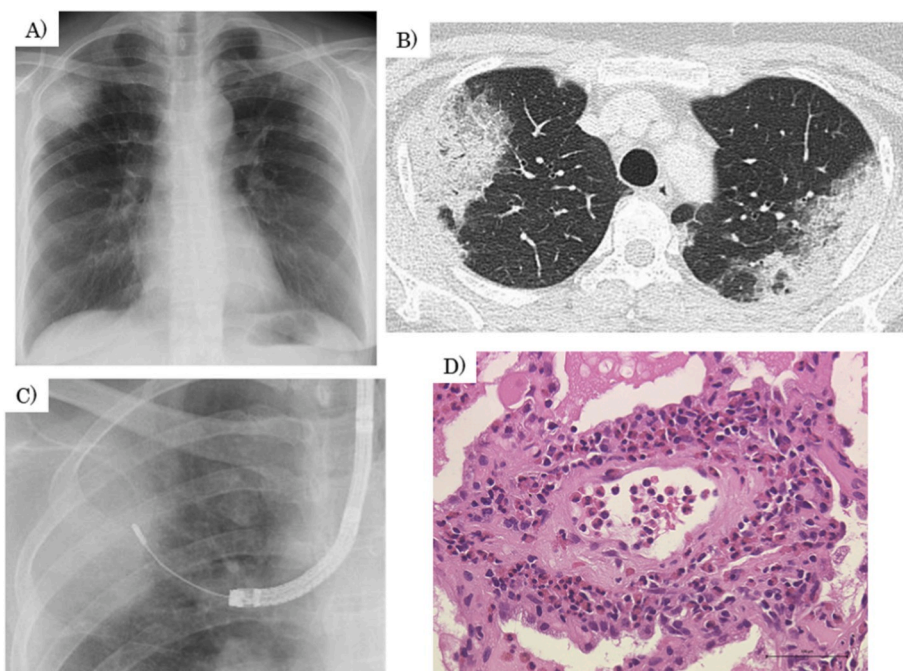


Fig. 1. Findings of chest images and pathology on first admission.

(A) Chest X-ray showed infiltrative shadows in the bilateral upper lung fields.

(B) Chest computed tomography (CT) showed consolidation and ground-glass opacity (GGO) in bilateral upper lobes.

(C) Bronchial cryobiopsy through fiberoptic bronchoscopy was performed in right B3a.

(D) Pathological specimen of cryobiopsy showed increased eosinophil infiltration in the alveolar space.

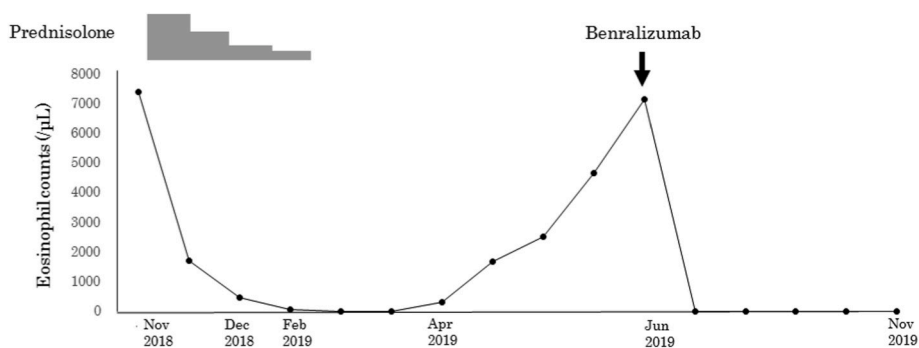


Fig. 2. Treatment and clinical course. The patient responded to prednisolone, and her peripheral blood eosinophil counts decreased. Peripheral eosinophil counts increased after prednisolone termination. After a single dose of benralizumab, her symptoms disappeared and the peripheral eosinophil count was zero.

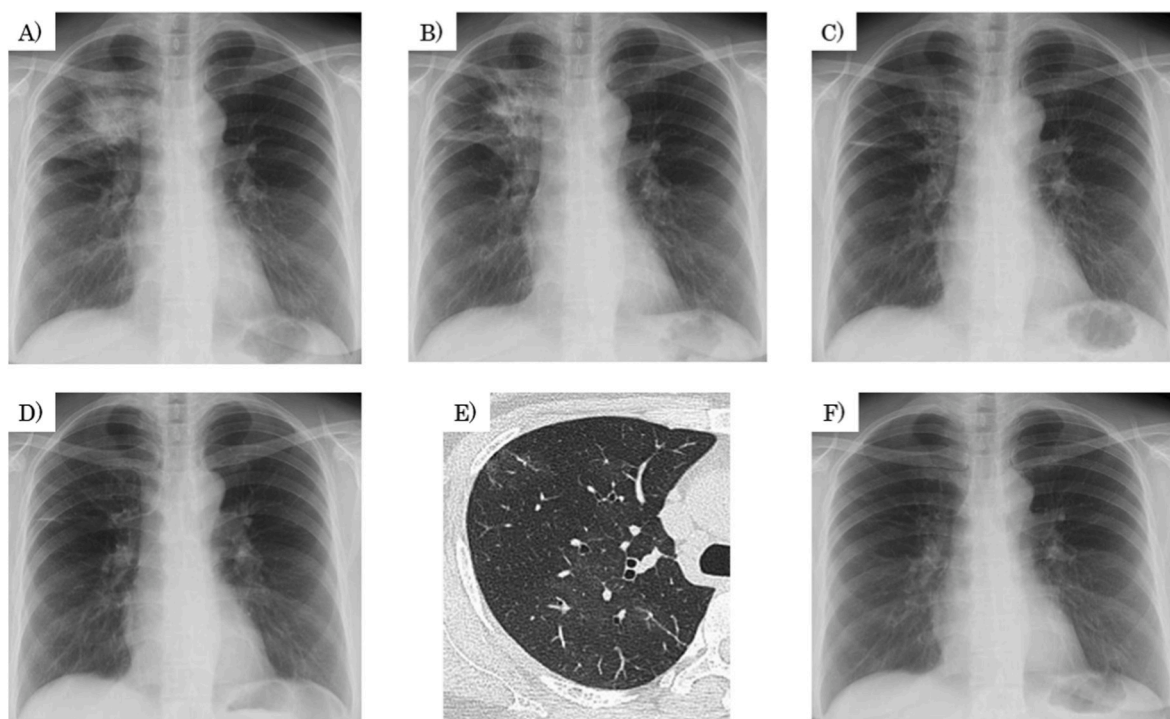


Fig. 3. Findings of chest images after a single dose of benralizumab for relapsed chronic eosinophilic pneumonia (CEP).

- (A) Chest X-ray showed a relapse of infiltrative shadows in the right upper lung field.
 (B) Abnormal infiltrates in the right upper lung field on chest X-ray showed ameliorations 1 week after administration of benralizumab.
 (C) Abnormal infiltrates in the right upper lung field on chest X-ray continued to show marked ameliorations 2 weeks after administration of benralizumab.
 (D) Chest X-ray shadow continued to be markedly ameliorated 1 month afterward.
 (E) Chest CT showed only slight ground-glass opacity (GGO) 1 month after benralizumab administration.
 (F) Chest X-ray showed no abnormal shadows at almost 6 months after benralizumab administration.

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Declaration of competing interest

All authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2020.101062>.

References

- [1] Y. Suzuki, T. Suda, Eosinophilic pneumonia: a review of the previous literature, causes, diagnosis, and management, *Allergol. Int. : Off. J. Jpn. Soc. Allergol.* 68 (4) (2019) 413–419.
- [2] E. Marchand, M. Reynaud-Gaubert, D. Lauque, J. Durieu, A.B. Tonnel, J.F. Cordier, Idiopathic chronic eosinophilic pneumonia. A clinical and follow-up study of 62 cases. The Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P), *Medicine* 77 (5) (1998) 299–312.
- [3] J. Durieu, B. Wallaert, A.B. Tonnel, Long-term follow-up of pulmonary function in chronic eosinophilic pneumonia, *Groupe d'Etude en Pathol. Interstitielle Soc. Pathol. Thorac. Nord Eur. Respir. J.* 10 (2) (1997) 286–291.

- [4] M. Naughton, J. Fahy, M.X. FitzGerald, Chronic eosinophilic pneumonia. A long-term follow-up of 12 patients, *Chest* 103 (1) (1993) 162–165.
- [5] R. Kolbeck, A. Kozhich, M. Koike, L. Peng, C.K. Andersson, M.M. Damschroder, J. L. Reed, R. Woods, W.W. Dall'acqua, G.L. Stephens, J.S. Erjefalt, L. Bjermer, A. A. Humbles, D. Gossage, H. Wu, P.A. Kiener, G.L. Spitalny, C.R. Mackay, N. A. Molfino, A.J. Coyle, MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function, *J. Allergy Clin. Immunol.* 125 (6) (2010) 1344–1353 e2.
- [6] T. Izumo, Y. Terada, M. Tone, M. Inomata, N. Kuse, N. Awano, A. Moriya, T. Jo, H. Yoshimura, Y. Furuhashi, Rapid effects of benralizumab on severe asthma during surgery for residual tumor after advanced lung squamous cell carcinoma treatment with pembrolizumab, *Respir. Med. Case Rep.* 26 (2019) 292–295.
- [7] W.W. Busse, R. Katial, D. Gossage, S. Sari, B. Wang, R. Kolbeck, A.J. Coyle, M. Koike, G.L. Spitalny, P.A. Kiener, G.P. Geba, N.A. Molfino, Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma, *J. Allergy Clin. Immunol.* 125 (6) (2010) 1237–1244 e2.
- [8] M. Laviolette, D.L. Gossage, G. Gauvreau, R. Leigh, R. Olivenstein, R. Katial, W. W. Busse, S. Wenzel, Y. Wu, V. Datta, R. Kolbeck, N.A. Molfino, Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia, *J. Allergy Clin. Immunol.* 132 (5) (2013) 1086–1096, e5.
- [9] T.H. Pham, G. Damera, P. Newbold, K. Ranade, Reductions in eosinophil biomarkers by benralizumab in patients with asthma, *Respir. Med.* 111 (2016) 21–29.
- [10] P.C. Fulkerson, M.E. Rothenberg, Targeting eosinophils in allergy, inflammation and beyond, *Nat. Rev. Drug Discov.* 12 (2) (2013) 117–129.
- [11] T. Yanagibashi, M. Satoh, Y. Nagai, M. Koike, K. Takatsu, Allergic diseases: from bench to clinic - contribution of the discovery of interleukin-5, *Cytokine* 98 (2017) 59–70.