# Long-Term Anti-Interleukin 5 Antibodies Treatment in a Patient with Chronic Eosinophilic Pneumonia

Shimizu Y[1], Kurosawa M[2], Sutoh Y[3], Sutoh E[2,3]

[1]Division of Respiratory Medicine, Kaminakai Family Clinic, Takasaki, Gunma, Japan

[2]Department of Allergy and Respiratory Medicine

[3]Department of Surgery, Sutoh Hospital, Annaka, Gunma, Japan

**Corresponding author:**

Motohiro Kurosawa

Department of Allergy and Respiratory Medicine, Sutoh Hospital, 3532-5 Annaka, Annaka, Gunma 379-0116, Japan

E-mail: motohiro@kl.wind.ne.jp



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**Palabras clave:** Benralizumab. Neumonía eosinofílica crónica. Anticuerpo anti-interleukina 5. Mepolizumab.

Chronic eosinophilic pneumonia (CEP), reported first by Carrington et al. [1], is an insidious lung disease, diagnosed with a triad of pulmonary symptoms, blood eosinophilia and chest radiographic abnormalities [2]. It is now typically diagnosed upon the combination of greater than 2-week pulmonary symptoms, bronchoalveolar lavage fluid (BALF) and/or blood eosinophila (usually with BALF cell count differential > 25 % or blood eosinophils > 1000/μL), and infiltrations on chest radiography [3,4]. Interleukin 5 (IL-5) is an essential cytokine in the development, maturation, activation and proliferation of eosinophils [5]. Consequently it could be a key element in the pathogenesis of CEP [6,7]. We present a patient with CEP treated with anti-IL-5 antibodies over 3 years.

A 58-year old female, diagnosed with asthma 1.5-year prior, visited the clinic because of increasing dyspnea on November 6, 1997. Since a few months before, she had cough, chest pain, anorexia, fatigue, malaise, and weight loss. On December 12, 1997, the laboratory data showed blood eosinophilia (1040/μL) and an elevated C-reactive protein (CRP) level (40.0 mg/L). She was thus hospitalized.

 
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Serum IgE levels was 1250 IU/mL, and specific IgE for *Dermatophagoides* were positive. Antineutrophil cytoplasmic antibodies were negative. Chest computed tomography (CT) showed infiltrative shadows in the right upper lobe (S2 regional predominance) and the left upper lobe (S3 regional predominance). Fiberoptic bronchoscopy showed normal findings. BALF analysis indicated increased percentage of eosinophils (eosinophils 77.0 %, lymphocytes 5.0 %, neutrophils 4.0 %, macrophages 14.0 %). Bacterial culture of BALF detected normal flora. Trans-bronchial lung biopsy (TBLB) specimens, obtained from the right upper lobe, showed an interstitial and alveolar eosinophilic predominance as well as foci of organizing pneumonia. Neither BALF nor TBLB specimens contained malignant cells. She was diagnosed with CEP.

She was given oral prednisolone 30 mg/day, which was tapered to 10 mg/day. Blood eosinophil count decreased (55 /μL), and CRP level dropped to normal levels. Chest CT showed ground-glass opacities were cleared. The patient declined to keep prednisolone therapy, and was discharged from the clinic on December 22, 1997. Nine years later, the patient returned to the clinic to receive treatment for CEP. She was treated with pranlukast 450 mg/day and prednisolone 10 mg/day orally, and daily use of budesonide/formoterol 160 μg/4.5 μg inhaler 2 puffs/day. Oral prednisolone was stopped 5 months after start of the therapy because of improvement of the symptoms. Her regimen had been constant except occasional treatments with systemic corticosteroid.

On October 15, 2015, she was introduced to the hospital by the experienced pulmonologist because of unstable respiratory symptoms, such as cough and increasing dyspnea, but not fatigue, malaise, and weight loss. Blood eosinophil count was 400/μL. Serum total IgE level was 262 IU/mL, and serum specific IgE for *Dermatophagoides*



 
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were positive. Her regimen was changed to prednisolone 10 mg/day and montelukast 10 mg/day orally, and daily use of budesonide/formoterol 160 μg/4.5 μg inhaler 4 puffs/day.

On April 28, 2016, she visited the emergency department. Blood eosinophil count was 1071/μL, and she was given aminophylline and hydrocortisone infusion (Figure 1). Budesonide/formoterol 160 μg/4.5 μg inhaler 8 puffs/day was prescribed. On May 6, blood eosinophil count was 1112/μL. Because of unstable respiratory symptoms, the patient was known to be compliant with oral prednisolone, and her inhaler technique was deemed adequate.

Mepolizumab was the first approved anti-IL-5 antibody for use in patients with severe eosinophilic asthma, and was launched in December 2015 in the 31 European countries covered by the European Medicine Agency (EMA). Recent case reports indicated favorable responses to mepolizumab in CEP [8,9]. However, the duration of mepolizumab therapy in these patients remains unclear.

Mepolizumab was administrated subcutaneously every 4 weeks, and drug safety was assessed at each visit. For monitoring of the control of CEP and asthma, eosinophils in peripheral blood were counted automatically, and forced volume capacity (FVC) and forced expiratory volume of 1 second ($FEV_1$) were measured in parallel with an assessment of Asthma Control Test (ACT) every 4 weeks. Chest CT examinations were performed as necessary.

Administration of 100 mg mepolizumab started on June 9, 2016. Blood eosinophil count was 231/μL. The percentages of predicted FVC and $FEV_1$, and the ACT score were 100.9 %, 73.3 % and 12. Chest CT showed ground-glass attenuations and nodular opacities in the right lower lobe (Figure 1-B supplementary), suggesting relapse of CEP



 
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in the patient. On July 7, blood eosinophil count decreased to 14/μL, but $FEV_1$ and the ACT score were 74.6 % and 14. On October 27, her $FEV_1$ improved to 76.7 % and her ACT score increased to 21. Chest CT showed no infiltrative shadows. She successfully withdrew from daily use of oral prednisolone. On June 22, 2017, blood eosinophil count, $FEV_1$ and the ACT score were 7/μL, 78.1 % and 25. She reduced daily dose of budesonide/formoterol 160 μg/4.5 μg inhaler to 4 puffs/day. Two-year administration of mepolizumab showed long-term management and persistent improvement of pulmonary function in the patient, and no side effects have been observed.

Benralizumab is a monoclonal antibody targeting the alpha chain of the IL-5 receptor, and its benefit was reached a longer dosing interval than mepolizumab [10]. On May 24, 2018, blood eosinophil count, FVC and $FEV_1$ were 12/μL, 115.0 % and 80.0 %. Because of the benefit, she hoped to be given 30 mg benralizumab every 4 weeks for the first 3 doses followed by every 8-week fixed-dose injection schedule. She had mild cough attacks in March 2019, but declined to be given systemic corticosteroid. Blood eosinophil count, $FEV_1$ and the ACT score were 112/μL, 74.3 % and 20. Chest CT showed no abnormal findings (Figure 1-E supplementary). So, she was given aminophylline infusion for 4 days. Since then, her pulmonary symptoms have been controlled, and will be followed up with benralizumab administration every 8 weeks.

Although recent case reports indicated favorable responses to mepolizumab in CEP [8,9], there is no evidence to suggest the recommended duration of anti-IL-5 antibodies therapy for either CEP or asthma. This is the first report of CEP with asthma controlled with long-term IL-5 antibodies treatment.



 
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**Conflict of interest**

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**Ethical disclosures**

Institutional ethics committee approved this study and written informed consent from each individual was obtained before the study.



 
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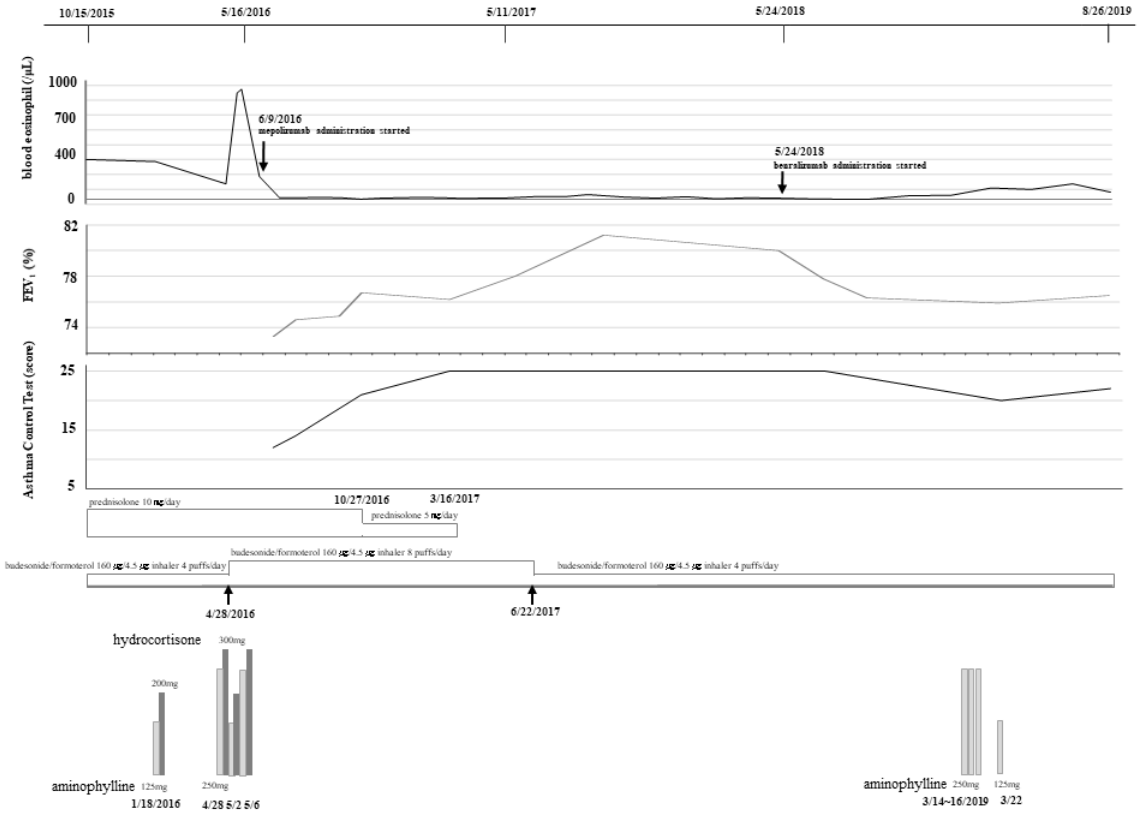
**Figure**

**Figure 1.** Clinical course of the patient diagnosed with chronic eosinophilic pneumonia and allergic refractory asthma. After start of monthly mepolizumab administration on June 6, 2016, she withdrew from daily use of prednisolone. In parallel with sustained reduction in blood eosinophil count, $FEV_1$ (%) values and ACT scores gradually improved with mepolizumab administration. On May 24, 2018, benralizumab administration was started. Her pulmonary symptoms have been controlled with anti-IL-5 antibodies treatment.

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