



## Case report

# Successful treatment of eosinophilic chronic rhinosinusitis and eosinophilic otitis media using the anti-IL-5 receptor monoclonal antibody benralizumab: A case report

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## ARTICLE INFO

Handling editor: Prof. B. Yawn

## Keywords:

Benralizumab  
Eosinophilic chronic rhinosinusitis  
Eosinophilic otitis media  
Anti-IL-5 receptor monoclonal antibody  
Asthma

## ABSTRACT

Eosinophilic chronic rhinosinusitis (ECRS) is characterized by the presence of nasal polyps, dominant ethmoid shadows in computed tomography (CT) scans, and elevated levels of eosinophil infiltration into the nasal polyps and peripheral blood. ECRS is often accompanied by severe asthma. The recent development of monoclonal antibody-based biologics, including benralizumab, has offered new therapeutic approaches for the treatment of asthma and allergic diseases. Asthma and ECRS are closely related; hence, benralizumab could provide clinical benefit in ECRS patients with severe asthma. Herein, we report a case of a 47-year-old female patient with severe asthma that presented with nasal obstruction and hearing impairment. Nasal endoscopic and otoscopic examinations indicated the presence of bilateral nasal polyps in the middle nasal meatus, as well as a bilateral effusion in the tympanic cavity. Sinus and temporal CT images showed dominant ethmoid sinus and tympanic cavity shadows. Biopsy of nasal polyps revealed high numbers of eosinophils, which led to the diagnosis of ECRS; eosinophilic otitis media (EOM) with hypereosinophilia was also suspected. Treatment with benralizumab reduced the number of peripheral blood eosinophils and improved asthma symptoms. Prolonged benralizumab administration also resulted in a remarkable size reduction in bilateral middle nasal polyps and aeration of the tympanic cavity. In conclusion, benralizumab treatment improved the symptoms of severe asthma, ECRS, and EOM. Eosinophil depletion could be an important mechanism by which benralizumab improves ECRS and EOM. The use of benralizumab for the treatment of ECRS and EOM patients with severe asthma merits further investigation in large-cohort studies.

## 1. Introduction

Eosinophilic chronic rhinosinusitis (ECRS), also known as chronic refractory sinusitis, is characterized by elevated levels of circulatory eosinophils, nasal polyps with eosinophil infiltration, and dominant shadow of ethmoid sinuses in computed tomography (CT) scans [1]. Patients with ECRS often show nasal congestion, loss of the sense of smell, increased mucus production, intermittent acute exacerbation after bacterial infection, and severe asthma [2]. Eosinophilic otitis media (EOM) is a type of intractable otitis media that occurs primarily in patients with asthma. EOM and ECRS have similar pathology [3]. Although systemic administration of corticosteroids can manage the

symptoms of ECRS and EOM, corticosteroid treatments often cause side effects [4]. Therefore, patients with ECRS frequently require endoscopic sinus surgery (ESS) [2]. Moreover, ECRS and EOM patients often relapse, requiring multiple surgeries or long-term administration of corticosteroids [2].

More recently, several biologics have been developed for the treatment of patients with severe asthma [5]. For example, anti-IgE and anti-interleukin (IL)-5 antibodies are currently being used clinically and have been shown to provide clinical benefit in patients with asthma. Benralizumab, an antibody targeting the IL-5 receptor (anti-IL-5R), was approved in 2018 for the treatment of patients with severe asthma in Japan [6]. Importantly, benralizumab has been shown to suppress

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<https://doi.org/10.1016/j.rmcr.2020.101135>

Received 29 April 2020; Received in revised form 16 June 2020; Accepted 16 June 2020

Available online 17 June 2020

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eosinophils and decrease their numbers in circulation and tissues. Herein, we report a case of a patient with severe asthma, ECRS, and EOM, who exhibited an impressive response to benralizumab treatment.

## 2. Case presentation

A 47-year-old female patient with severe bronchial asthma visited our department after experiencing nasal discharge, nasal obstruction, and hearing impairment. The patient was diagnosed with asthma at the age of 27 and had been receiving treatment with antihistamine, montelukast, regular-dose inhaled corticosteroids (ICSs), and long-acting beta-agonist (LABA). Furthermore, the patient had received systemic treatment with corticosteroids when an acute asthma exacerbation occurred approximately 1 month prior to admission to our department. Peripheral blood tests showed that eosinophils constituted as much as 14.7% of blood cells. At the age of 36, the patient also experienced nasal discharge, nasal obstruction, and hearing loss; she was treated at a different clinic, yet her symptoms did not improve. At admission to our department, nasal endoscopy findings showed large polyps in the bilateral middle nasal meatus (Fig. 1A), while otoscopic findings revealed bilateral effusion in the tympanic cavity. We also observed dominant soft-tissue shadows, in the ethmoid sinus (Fig. 2A) and tympanic cavity in sinus and temporal CT scans, respectively. Biopsy of the nasal polyps revealed the presence of more than 200 eosinophils in a 400-fold visual field; thus, the patient was diagnosed with ECRS. EOM was also suspected based on the medical history of the patient; however, she did not receive myringotomy due to moderate hearing loss. In addition to treatment for asthma, the patient received oral administration of clarithromycin and L-carbocysteine for EOM. Despite the high-dose ICS and systemic corticosteroid administration, her asthma was poorly controlled because of repeated exacerbation and relapse. Therefore, a respiratory physician decided to treat the patient with benralizumab (30 mg/body, subcutaneous administration once every 4 weeks).

At the beginning of benralizumab treatment, the nasal symptoms and hearing impairment had not improved, and the patient did not receive additional treatment for ECRS. One month after the initiation of benralizumab treatment, the rate of peripheral blood eosinophilia

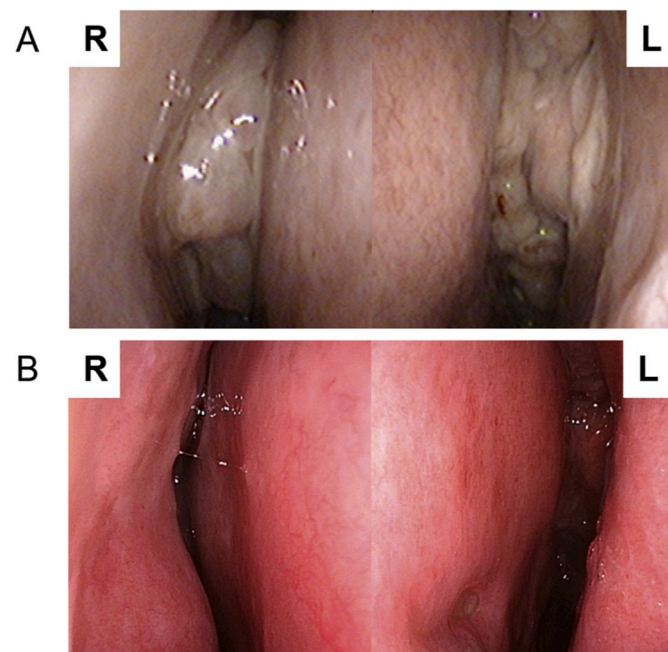


Fig. 1. Intranasal endoscope findings prior to benralizumab treatment (A) and 4 months after benralizumab treatment (B).

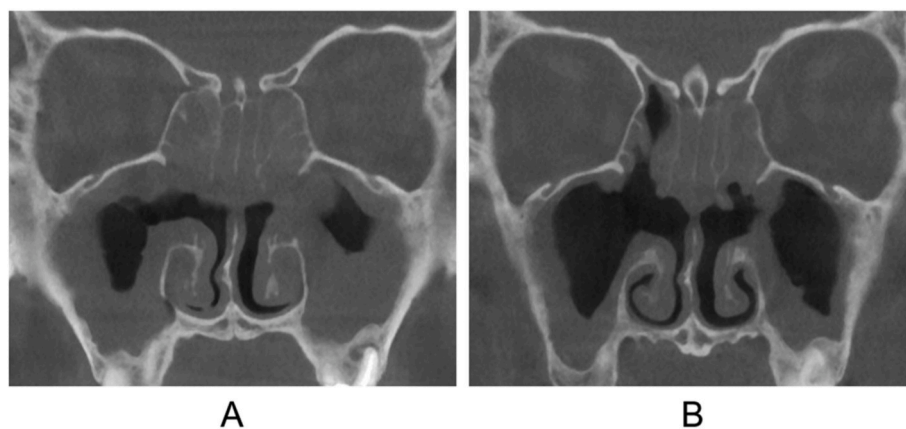
dramatically decreased to 0%. Two months after the initiation of benralizumab treatment, the patient reported that the hearing impairment worsened. Otoscopic findings revealed bilateral effusion in the tympanic cavity (Fig. 3A). A pure tone audiogram showed 35.0 dB (right) and 40.0 dB (left) and suggested mixed hearing loss (average of 500, 1000, 2000, and 4000 Hz) (Fig. 4A). Tympanometry revealed a type B curve in the right ear and type C curve in the left ear. Myringotomy was performed in both ears (Fig. 3A), and a tympanostomy tube was inserted in the left tympanic membrane to treat highly viscous middle ear effusion (MEE) in the tympanic cavity. Cytological examination of viscous MEE revealed the absence of infiltrated eosinophils.

Three months after the initiation of benralizumab treatment, nasal symptoms improved subjectively, and no marked change in the condition of the bilateral middle nasal polyps was observed. However, a biopsy of the nasal polyps revealed no eosinophils in a visual field at 400× magnification, suggesting complete elimination of eosinophils in the nasal polyps. Regarding the ear symptoms, the bilateral hearing levels had improved subjectively, and the tube naturally fell out of the left ear. Highly viscous MEE from the right ear contained no eosinophils.

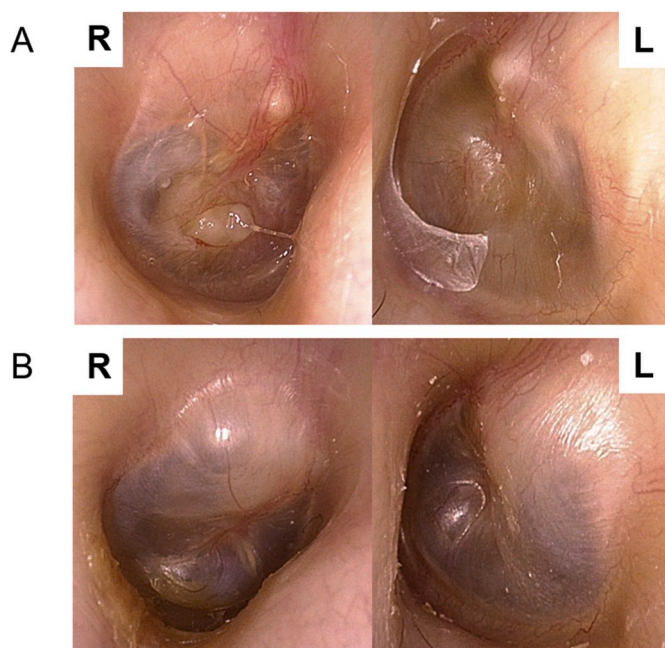
Four months after the initiation of benralizumab treatment, nasal endoscopy indicated a remarkable reduction in the size of bilateral nasal polyps and improvement of nasal obstruction (Fig. 1B). Although MEE improved, myringotomy was repeated due to eardrum retraction. Sinus CT scans showed that the soft-tissue density shadows in the bilateral ethmoid sinus and maxillary sinus decreased in size (Fig. 2B). One month later, otoscopy revealed the absence of bilateral middle ear effusion (Fig. 3B), and the hearing impairment had improved (Fig. 4B). Temporal CT images revealed that the soft-tissue density shadows in the bilateral tympanic cavity also decreased in size. Additionally, asthma symptoms improved, and the eosinophil count remained 0%. Throughout the treatment, the patient was closely monitored for ECRS symptoms; no additional treatments such as ESS and intranasal steroid therapy were required. Neither asthma attack nor exacerbation of nasal symptoms occurred after the initiation of benralizumab treatment. The patient's clinical condition should be followed for a long time; however, no additional treatment was needed at the time of writing this report.

## 3. Discussion

The patient presented here was diagnosed with ECRS, and EOM was suspected. Benralizumab could potentially be used for the treatment of ECRS and EOM as an alternative to surgery or long-term systemic administration of corticosteroids. The reduction of eosinophil numbers after benralizumab treatment could result in nasal polyp size reduction and the improvement of MEE, nasal congestion, nasal discharge, and hearing impairment. Elevated levels of circulatory eosinophils and tissue eosinophils are important features of ECRS pathogenesis. Enzymes and proteins released by eosinophils can damage tissues and drive the development of nasal polyps [7], resulting in nasal obstruction and nasal discharge in patients with ECRS [2]. Histological examination of the MEE from patients with EOM typically reveals an increased number of eosinophils and a large amount of mucin, indicative of eosinophilic inflammation in the middle ear [3]. Although multiple cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, IL-4, IL-13, IL-17, IL-22, and IL-33, are involved in the eosinophilic inflammation in ECRS [2,8], IL-5 is the most important cytokine regulating the differentiation, proliferation, survival, and activation of eosinophils [9]. IL-5R is present on the cell surface of eosinophils, basophils, and mast cells [10]. IL-5 has a high affinity for IL-5R and is the only cytokine that activates IL-5R. The anti-IL-5R antibody, benralizumab is a humanized afucosylated monoclonal antibody that strongly binds to an epitope in domain 1 of the  $\alpha$  subunit of IL-5R. Benralizumab administration induces the robust and nearly complete depletion of eosinophils by natural killer cells through antibody-dependent cell-mediated cytotoxicity [11]. Benralizumab has a wide range of effects, including eosinophil depletion within 24 hours of administration,



**Fig. 2.** Nasal computed tomography (CT) images. (A) CT scan prior to benralizumab treatment showed a soft-tissue density shadow extending from the maxillary sinus to ethmoid sinus. (B) CT scan at 4 months after benralizumab treatment showed that the soft-tissue density shadow decreased in size, both in the maxillary sinus and ethmoid sinus.



**Fig. 3.** Otolaryngoscopic findings at 2 months (A) and 5 months (B) after benralizumab treatment.

reduction in the numbers of circulating eosinophils to below the detection limit, and almost complete elimination of airway mucosal eosinophils [11].

Thus, anti-IL-5 and anti-IL-5R antibodies play important roles in the treatment of diseases caused by eosinophilia. Anti-IL-5 antibodies such as mepolizumab and reslizumab have been reported to be effective against ECRS [12–14]. However, the use of mepolizumab or reslizumab is not approved for ECRS or EOM. It has also been reported that benralizumab is effective against ECRS and EOM alone [15,16]; however, this is the first report to show that benralizumab is effective against both ECRS and EOM simultaneously. In the presented case, these mechanisms might have contributed to the reduction in the numbers of eosinophils in the circulation and tissues, and the subsequent improvement of nasal obstruction, nasal discharge, and hearing impairment.

In the present case, the numbers of eosinophils in the circulation and tissues may have decreased immediately after the start of benralizumab treatment; however, the onset of action of benralizumab was delayed for both ECRS and EOM. Subjective symptom relief in ECRS and EOM was

achieved 3 months after the initiation of benralizumab treatment. In addition, endoscopic findings in ECRS and otoscopic findings in EOM had sufficiently improved by 4 and 5 months after the initiation of benralizumab treatment, respectively. In a double-blinded phase II trial performed in Japan evaluating the effect of benralizumab on ECRS, benralizumab or placebo was administered three times every 4 weeks over the course of 3 months [17]. Although the blood eosinophil count reached zero after benralizumab treatment, similar to the present case, there were no significant differences in the nasal polyp score between the benralizumab and placebo groups at 3 months after the start of treatment relative to baseline. In this double-blinded phase II trial, the duration of benralizumab treatment may have been too short to allow sufficient effects. Although the onset of action of benralizumab was relatively slow for ECRS and EOM in the present case, benralizumab was administered for more than 5 months, resulting in sufficient effects of benralizumab on symptom relief and endoscopic and otoscopic findings in ECRS and EOM. In addition, the delay in the otoscopic improvements may have been related to the time associated with the change to highly viscous MEE.

ECRS patients who do not benefit from antihistamines, montelukast, and systemic administration of corticosteroids typically undergo endoscopic sinus surgery (ESS); however, ECRS patients often relapse and require multiple surgeries or long-term administration of corticosteroids [2]. Performing multiple operations in the nasal cavity and paranasal sinuses are technically challenging and increase the risk of postoperative complications. Moreover, the symptoms of EOM do not always improve with conventional therapeutic interventions, including myringotomy and insertion of a tympanostomy tube. Considering that the increase in the levels of circulatory and tissue eosinophils is closely related to the pathology of ECRS and EOM, it is extremely challenging to treat these conditions solely with surgery. Therefore, the development of novel drugs that suppress eosinophil recruitment and activation is needed. The efficacy of biologics in patients with ECRS has been investigated in several studies [18]; among these biologics, anti-IgE and anti-IL-5 antibodies have emerged as the most promising agents for the treatment of ECRS and EOM [19,20]. In the case presented here, benralizumab improved the nasal and ear symptoms of the patient, suggesting that benralizumab could be a promising treatment choice for refractory ECRS and EOM, even in patients with severe asthma.

In conclusion, benralizumab treatment reduced the size of nasal polyps in a patient with ECRS and was involved in the improvement in MEE. Benralizumab also improved the nasal, ear, and respiratory symptoms. Therefore, benralizumab therapy could serve as a useful therapeutic approach for the treatment of refractory ECRS and EOM in patients with severe asthma.

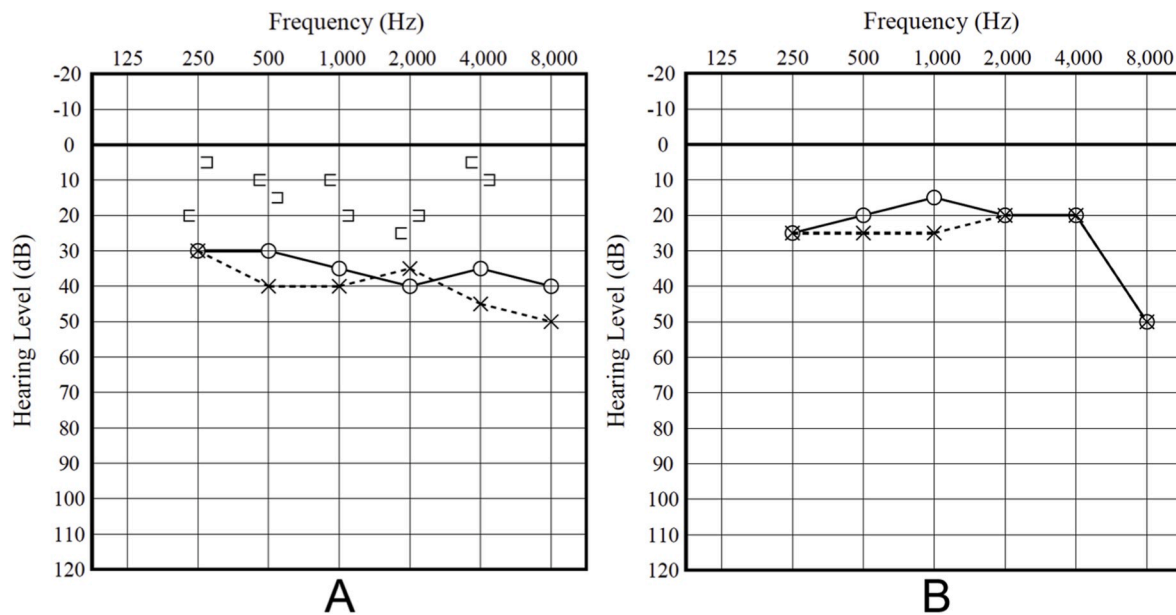


Fig. 4. Pure tone audiometry results at 2 months (A) and 5 months (B) after benralizumab treatment. The air-bone gap reduced in size in both ears.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2020.101135>.

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