Respiratory Medicine Case Reports 32 (2021) 101336

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Rapid and remarkable effectiveness of benralizumab for treating severe bronchial asthma with intractable eosinophilic rhinosinusitis and eosinophilic otitis media: A case report

Hideyasu Shimizu [a,b], Hisayuki Kato [c], Satoshi Yoshioka [c], Mitsushi Okazawa [b,d,*]

[a] Toshiwakai Clinic, Nagoya Japan, Nagoya, Japan
[b] Department of Medicine, Division of Respiratory Medicine and Clinical Allergy, Fujita Health University, Toyoake, Japan
[c] Department of Otolaryngology-Head and Neck Surgery, Fujita Health University, Toyoake, Japan
[d] Department of Respiratory Medicine, Daiyukai General Hospital, Daiyukai Health System, Ichinomiya, Japan

ARTICLE INFO

Keywords:
Severe asthma
Eosinophilic chronic rhinosinusitis
Eosinophilic otitis media
Benralizumab
QOL

ABSTRACT

Severe bronchial asthma is a challenging disorder to treat and can impair quality of life (QOL) under conventional therapeutic modalities. We report the case of a 52-year-old woman with severe asthma associated with eosinophilic chronic rhinosinusitis (ECRS) and eosinophilic otitis media (EOM). Although the patient was treated with a full dose of inhaled corticosteroid, leukotriene receptor antagonist (LTRA), theophylline, burst use of oral corticosteroids (OCS), her asthmatic condition aggravated, disrupting her daily life. ECRS and EOM symptoms were also getting worse despite treatment with topical application of corticosteroids to the nose and ears, LTRA, and occasional use of OCS. In addition to asthmatic symptom, the patient always suffered from intractable nasal obstruction and hearing disturbance, which contributed to the heavily impaired QOL. However, the administration of benralizumab showed rapid and remarkable improvement not only in her asthmatic conditions but also in the symptoms of ECRS and EOM within a month. These results suggest that the use of benralizumab for the treatment of severe asthma with intractable ECRS and EOM should be considered when the patient's QOL is severely deteriorated.

1. Introduction

Severe asthma is defined as a condition that is uncontrolled despite adherence to maximal optimized therapy and treatment of contributory factors and that worsens when high dose treatment with corticosteroids is decreased [1]. It results in physical, mental, and emotional stresses, with compromised quality of life (QOL), resulting in socioeconomic burden. Eosinophilic chronic rhinosinusitis (ECRS) and eosinophilic otitis media (EOM) have drawn attention in the 1990s as new disease entities that are difficult to treat. Patients with ECRS exhibit multiple nasal polyps on both sides with severe eosinophils, olfactory disturbance, and sinusitis with more fluid accumulation in the ethmoid sinuses than other sinuses [2]. EOM occurs mostly in women in their 50s and complicates with ECRS and severe asthma [3]. Accumulation of highly viscous effusion and granulation with eosinophil infiltration in the middle ear bulge the eardrum and frequently perforate it, causing a hearing disturbance. Although conventional treatments such as leukotriene receptor antagonist (LTRA), mucoregulator, macrolide antibiotics, and topical application of corticosteroids are used for treating both ECRS and EOM, these conditions are usually resistant to treatments requiring oral corticosteroids (OCS) and recurs frequently when treatment is reduced [2,3]. ECRS and EOM are reported to coexist, and symptoms such as the stuffy nose, headache caused by nasal polys, accumulation of fluid in sinuses, and hearing disturbance caused by eardrum perforation can contribute to the impaired QOL of patients with severe asthma. This study reports a middle-aged woman whose severe asthma with intractable ECRS and EOM was remarkably relieved using benralizumab.

Abbreviations: QOL, quality of life; ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; ADL, activity of daily living; AR, allergic rhinitis; SMART, single maintenance and reliever therapy; FeNO, Fractional exhaled nitric oxide; CT, computed tomography; JESREC, Japanese epidemiological survey of refractory eosinophilic rhinosinusitis; BMI, body mass index.

* Corresponding author. Department of Respiratory Medicine, Daiyukai general Hospital, Daiyukai Health System, 1-9-9, Sakura, Ichinomiya. Japan.
E-mail address: mokazawa@fujita-hu.ac.jp (M. Okazawa).

https://doi.org/10.1016/j.rmcr.2020.101336
Received 1 July 2020; Received in revised form 8 December 2020; Accepted 26 December 2020
Available online 31 December 2020

2. Case report

A 52-year-old woman was referred to our clinic for the treatment of severe asthma with ECRS and EOM restricting activity of daily living (ADL). She had been suffering from nasal stuffiness and runny nose from her teens. She was diagnosed with allergic rhinitis (AR), and was treated using corticosteroid nasal spray and anti-allergic oral medications once a while when she had severe symptoms. In her mid-thirties, the patient realized loss of sense of smell and development of nasal obstruction owing to nasal polyps on both sides, which were required to be removed. Four palliative operations were performed for limiting the enlargement of polyps and for opening sinuses as much as possible. However, severe bleeding occurred in each operation, and the polyps recurred. The patient was treated with corticosteroid nasal spray and long-term oral erythromycin with little improvement in symptoms. Computed tomography (CT) images of the sinuses showed that the ethmoidal and maxillary sinuses were filled with fluid (Fig. 1A). Pathological examination of the excised polyp revealed numerous eosinophils, scattered lymphocytes, and plasma cells, as depicted in Fig. 1B. The number of eosinophils in the tissue obtained from three different subepithelial areas was 240 on average observed under a high-power field of a light microscope (× 400). At 45 years old, the patient experienced a sudden onset of dyspnea, cough, and wheezing, and these conditions worsened in the night and in the early morning. She was diagnosed with adult-onset bronchial asthma by a general physician and was treated with fluticasone/salmeterol (ADVAIR500®) inhalation. Although ADVAIR500® was effective for 2–3 years as maintenance therapy, asthmatic symptoms gradually aggravated, and single maintenance and reliever therapy (SMART) of budesonide/formoterol (SYMBICORT200®)was administered 8–12 times/day. Since exacerbation of asthma frequently occurred in the past two years with the use of SMART, oral prednisone (30 mg/day) for one week was prescribed once every 1–3 months. As the asthmatic symptom worsened, the patient had ear discharge on both sides and difficulty in hearing high-pitched tones such as the ringing of a beeper. Otoscopic examination showed a perforation of the eardrum on both sides and a highly viscous yellowish colloid discharge oozing from the middle year (Fig. 1C). Since the discharge was very thick and sticky, aspiration and insertion of the ventilation tube were not effective. The smear of the discharge showed eosinophil infiltration (Fig. 1D). Ear drops of 10 mg triamcinolone were frequently used with increased discharge, but the effectiveness was limited, and oral betamethasone/chlorpheniramine tablets were used once a while for symptom relief. During her latest exacerbation of asthma two months ago, her asthma condition and QOL evaluated using the Asthma Control Test [4] and mini Asthma Quality of life Questionnaire [5] became the worst ever and dyspnea on exertion prevented her from walking 30 m without resting (Table 1). The patient received 30 mg of oral prednisone and 12 times inhalation of SYMBICORT200®, montelukast, and theophylline. Although asthmatic control returned to the previous condition with three weeks of oral prednisone treatment, nasal symptoms and ear discharge increased again after withdrawal of prednisone. Since severe asthma, ECRS, and EOM were uncontrollable, the patient was referred to our clinic for treatment using biologics (Table 1). Since blood eosinophil count and exhaled nitric oxide (FeNO) were very high (898/μl and 113 ppb, respectively) and IgE was low (80 IU), benralizumab was administered for deactivation of eosinophils. One month after the administration of benralizumab, asthmatic condition, QOL, and pulmonary function improved dramatically (Table 1), and inhalation of SYMBICORT200® four times a day was sufficient for maintaining asthmatic conditions. Sinus symptoms also dramatically improved, and colloid ear discharge disappeared. Sinus CT and an otoscopic view of the left eardrum after treatment with benralizumab are presented in Fig. 2A, C. Fluid in the ethmoidal sinus was greatly decreased in both sides, although accumulation of fluid in both maxillary sinuses remained. The perforation of the eardrum was completely closed (Fig. 2C). Benralizumab was administered once a month for the first three months and was continued bimonthly. Four months after the first administration of benralizumab, the patient showed mild asthmatic symptoms after catching a cold. However, rapid recovery was achieved by increasing SYMBICORT200® inhalation. Five months after the administration of benralizumab, a fifth polypectomy was performed. Unlike the previous four operations, polyps significantly shrank, and effective removal of

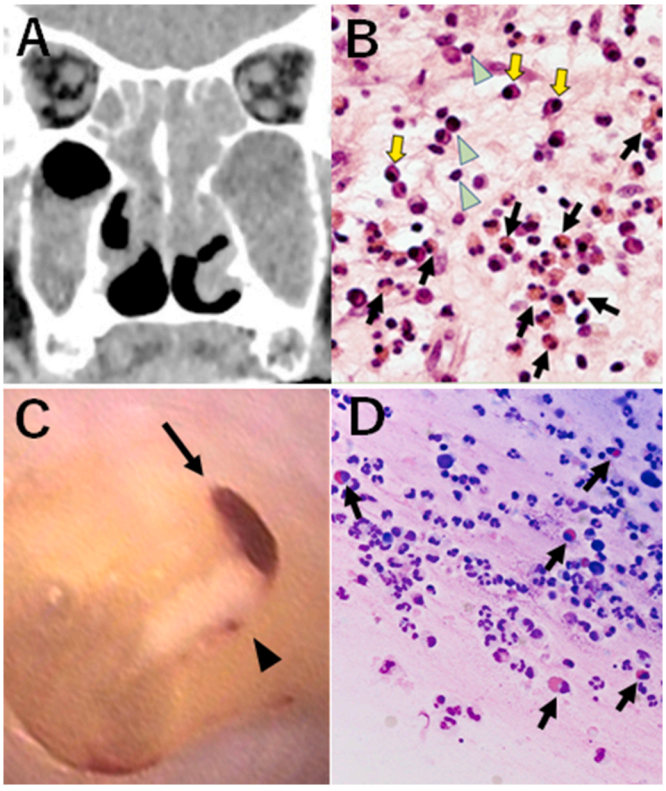

Fig. 1. Before benralizumab treatment. A: Coronal section of sinus computed tomography. Both sides of the ethmoidal and maxillary sinuses were filled with fluid. B: Pathological section of nasal polyp stained with hematoxylin and eosin. Numerous eosinophilic leucocytes (black arrows), scattered lymphocytes (yellow arrows), and plasma cells (green arrowheads) were observed. C: Otoscopic picture of the left eardrum. Sticky yellowish discharge (black arrowhead) occurred from a perforation of the left eardrum at the upper corner (black arrow). D: Giemsa staining of ear discharge. Eosinophils were observed (black arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Asthma control, QOL and Laboratory data.

			Period after benralizumab administration(months)			
	Latest exacerbation	First visit	1	2	4	6
ACT	5	14	23	25	20	25
Mini AQLQ	2.8	3.8	6.4	6.6	6.4	6.6
FEV_1(L)/ FEV_1/FVC (%)	N/A	1.29/ 72.5	1.96/ 83.8	1.99/ 82.9	1.87/ 83.9	1.96/ 82.4
WBC	N/A	7300	5300	7200	5700	N/A
Eosinophils (%)	N/A	12.3	0.2	0.7	0.1	N/A
FeNO (ppb)	N/A	113	26	24	20	17

Two months before and 6 month period after benralizumab administration. ACT: asthma control test [5], AQLQ: asthma quality life questionnaire [6], FEV_1: forced expiratory volume in one second, FEV_1/FVC: FEV_1 divided by forced vital capacity, WBC: white blood cell count, eosinophils: percentage eosinophils count in WBC, FeNO: Fractional exhaled nitric oxide.

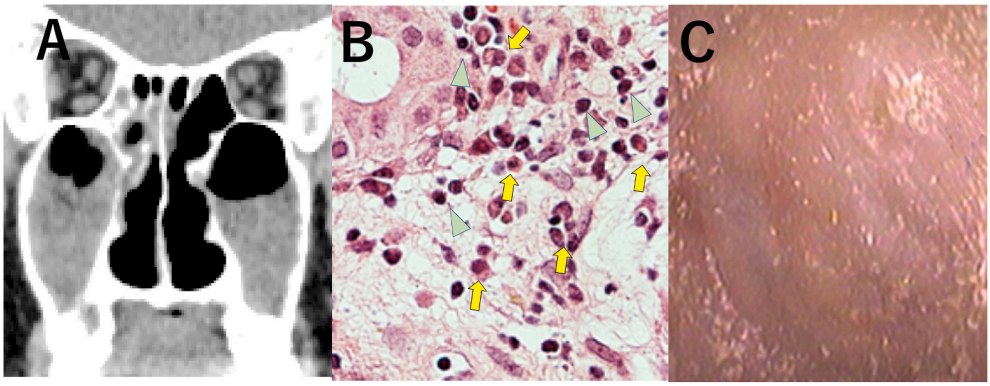

Fig. 2. Two months after administration of benralizumab. A: Coronal section of sinus computed tomography. Fluid in the ethmoidal sinus was dramatically reduced and aeration was found in both maxillary sinuses. B: Pathological section of the nasal polyp stained with hematoxylin and eosin. Eosinophils disappeared and cellular infiltration was mostly lymphocytes (yellow arrows) and plasma cells (green arrowheads). C: Otoscopic picture of the left eardrum. A hole in the eardrum closed, and was covered with normal epithelium. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

polyps was achieved for both sides because of limited bleeding during the operation. Pathology of the specimen showed disappearance of eosinophils (Fig. 2B). Currently, she is receiving a bimonthly benralizumab injection, and improvement in her physical condition made it possible for her to jog every day. Although her sense of smell did not completely recover, she could smell most of the food items. Hearing loss also improved, and she could hear a beeper.

3. Discussion

This report showed that administration of benralizumab conferred a rapid and marked improvement in a patient with severe asthma with intractable ECRS and EOM. In contrast, one of the major limitations impeding the use of benralizumab is its high cost, which needs to be addressed. The active definition of severe asthma is the condition that asthmatic symptoms are difficult to control despite global initiative for asthma (GINA) step 4–5 treatment with good adherence and inhaler technique [1,6]. The prevalence of severe asthma in Japan is 7.8% (severe controlled asthma, 5.3% and severe uncontrolled asthma, 2.5%), which is similar to that in western countries [7,8]. Our patient was diagnosed with severe and uncontrolled asthma because good adherence and adequate inhalation technique of high dose inhaled corticosteroid with administration of LTRA, theophylline, and OCS burst therapy (once every 1–3 months) failed to control her asthmatic condition, and her ADL deteriorated (Table 1). Cluster analysis for severe adult asthma have reported several phenotypes in severe asthma, such as early-onset allergic asthma, late-onset asthma associated with obesity, late-onset neutrophilic asthma, or late-onset eosinophilic asthma [9–11]. Our patient is non-atopic since her IgE level was low and no specific antigens were detected (Table 1). Although obesity is also one of the risk factors for developing severe asthma [12], the impact of obesity on severe asthma in Japan may be lower than that in western countries since only 5–7% of patients with severe asthma have a body mass index (BMI) of >30 kg/m2 [7]. The BMI of our patient was 20.8 when she visited our clinic, and she reported no obesity in her life. Pathological examination of nasal poly showed the infiltration of numerous eosinophils, without neutrophils in the submucosa (Fig. 1B), and the patient had a very high FeNO level. Since asthma appeared in her mid-40s, the patient's phenotype can be categorized as late-onset eosinophilic severe asthma. Soma et al. investigated patients with severe asthma in Japan using FeNO and eosinophil counts in peripheral blood as surrogate markers of type 2 inflammation [13]. They found that increased FeNO and eosinophil counts in peripheral blood were significant predictors of frequent exacerbation and impaired asthma control, as observed in our case. More than 80% of patients with severe asthma in Japan have type 2 inflammation [14].

A multi-institutional study of asthmatic patients in Japan showed that 66.2% of asthmatic patients had rhinitis, and patients with uncontrolled asthma had rhinitis more frequently than those with controlled asthma [15]. Our patient had AR-compatible symptoms in her teens. Although the patient is currently non-atopic, she might have been atopic in her teens, and she reported that treatment using anti-allergic medications and topical application of corticosteroid had been very effective. As our patient reached her 30s–40s, rhinosinusitis with nasal polyps developed. Sinusitis with/without aspirin intolerance is important comorbidities of difficult to treat asthma [1,16]. The recurrence of nasal polyps after endoscopic sinus surgery was reported to be closely related to the development of bronchial asthma, increased eosinophil levels in peripheral blood, and fluid accumulation, especially in the ethmoid sinus observed using CT, as shown in our patient [2] Since increased infiltration of eosinophils in the mucosa of nasal polyps or ethmoid cavities is thought to be a strong promoter of refractoriness to the treatment [17], the Oto-Rhino-Laryngological Society of Japan established a Japanese epidemiological survey of refractory eosinophilic rhinosinusitis (JESREC). JESREC issued the diagnostic criteria for eosinophilic chronic rhinosinusitis by scoring four factors: unilateral or bilateral disease, presence of nasal polyps, blood eosinophilia, and dominant shadow in the ethmoid sinus [2]. Our patient had bilateral sinus disease (Fig. 1 A) with bilateral nasal polyps and blood eosinophilia (Table 1), fulfilling the criteria for confirming ECRS. Severe bronchial asthma and ECRS are closely related to each other and have a background of type 2 inflammation [16].

EOM is another phenotype of type 2 inflammation associated with severe asthma [3]. EOM is a fairly new entity of middle ear disease with a highly viscous yellowish effusion containing numerous eosinophils as shown in Fig. 1C and D. Although conductive hearing impairment is the initial stage, as in our case, the gradual progression of the disease can lead to deafness [18]. Based on the diagnostic criteria for eosinophilic otitis media [3], our case had major factors of intractable otitis media with adult-onset severe bronchial asthma and glue-like effusion with eosinophilic infiltration (Fig. 1D) resistant to conventional treatments, such as insertion of the tympanic ventilation tube. Since our patient with uncontrolled severe bronchial asthma developed hearing disturbance owing to EOM and nasal symptoms owing to ECRS, her QOL was extremely impaired (Table 1).

It has been documented that optimal control of asthma improved EOM or AR [19–21], and these reports led us to postulate "one airway, one disease". In our patient, the onset of airway disease started with AR in her early life, followed by ECRS in middle age. Although it took almost 35 years to reach this condition, the development and aggravation of bronchial asthma were rapid and profound. The structural changes in airways induced by type 2 inflammation could intensely contribute to the development of airway hyperresponsiveness and exaggerated airway narrowing, directly causing dyspnea [22].

Since our patient developed uncontrolled severe bronchial asthma along with ECRS and EOM, she experienced difficulty in walking a long distance without a rest or doing daily housework; therefore, biologic administration was planned. Since her airway and ear inflammation

might be related to type 2 inflammation and her IgE level was low, anti-IL-5 biologic therapy was selected for the add-on therapy as recommended by GINA [1]. Benralizumab, an monoclonal antibody to IL-5 receptor α (IL-5Rα) on eosinophils and also binds the RIIIa region of the FCγ receptor (FcγRIIIa) on natural killer cells, macrophages and neutrophils with a high affinity [23], was used in our case, and nearly complete depletion of eosinophils in the peripheral blood was achieved through enhanced antibody-dependent cell-mediated cytotoxicity [24]. Following depletion of eosinophils in the peripheral blood, asthma control, asthma-related QOL, and pulmonary function dramatically improved in a month (Table 1). Similar improvement in ECRS and EOM was observed after treatment with benralizumab. The nasal polyps shrank and were easily removed by operation without any problems. Eosinophil infiltration in nasal polyps also completely disappeared with scattered lymphocytes and plasma cells (Fig. 2B). Although it was gradual, the perforation of the eardrum was closed (Fig. 2C), and hearing impairment disappeared. Since most of the long-standing airway and ear symptoms disappeared in a month following the administration of benralizumab, inflammation of the upper and lower airways and the middle ear in our case could largely be caused by the IL-5 dependent eosinophilic type 2 inflammation. Benralizumab binds to the IL-5Rα receptor on eosinophils, inhibiting bone marrow differentiation and maturation, cell adhesion and migration, release of granule proteins, and promotes cell survival. This antibody also binds to the FcγRIIIa receptor on natural killer cells, macrophages, and neutrophils, inducing antibody-dependent cellular cytotoxicity to eosinophils. This double-function, which is different from other IL-5 antagonist such as mepolizumab and reslizumab [23], might have induced the near-complete deletion of eosinophils from the patient's airways and provided rapid symptomatic relief. Although therapy with anti-IL-5 antibodies are greatly effective for treating type 2 inflammation by suppressing eosinophilic infiltration [23,24], the bottle neck of using these drugs is the high cost of treatment. The official cost of benralizumab is 358,045 Japanese yen (~3400 US dollar) for one ampule (30 mg), which is used once per month for the first 3 months, and bimonthly thereafter. Although Japan has a system of public health insurance for the whole nation, only a small number of patients can afford this cost since most patients have to pay 30% of the cost, including treatment and medicine, except those with no income or low-income individuals over 70 years of age. In contrast, rare and intractable diseases, including ECRS, are designated as the designated intractable diseases by law through careful examination, laboratory testing, and histological examination if necessary, for diagnoses to fulfil the criteria [25,26]. For a patient with a designated intractable disease, all cost is deducted to a maximum of 20000–30000 Japanese yen (190–290 US dollars) per/-month depending on patient's income; the remaining cost is covered by public expense. Since our case fulfilled the criteria for ECRS, the patient is continuously using benralizumab and is in excellent condition, not only with regard to ECRS but also for severe bronchial asthma and EOM.

4. Conclusion

In summary, we encountered a case in which benralizumab showed a rapid and dramatic improvement in asthma control and symptoms of ECRS and EOM. The administration of anti-IL-5 biologic could be the best add-on therapy for intractable type 2 inflammation in the upper and lower airways and the middle ear. Public financial support, however, must be mandatory for effective use of IL-5 antagonist therapy.

Informed consent statement

Written informed consent was obtained from the patient.

Author contributions

H.S. is the doctor in-charge for this patient and wrote this manuscript under the supervision of M.O. H.K. and S.Y. are doctors in-charge for sinus surgery.

Funding

Research fund of Toshiwakai Health System, Japan.

Declaration of competing interest

The authors report no conflict of interests.

Acknowledgement

We greatly appreciate the medical staff of Toshiwakai clinic for their dedicated work to treat patients.

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