Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
OPEN ACCESS

Assessment of the rapid effect of dupilumab in two cases of severe asthma comorbid with recurrent eosinophilic chronic rhinosinusitis after endoscopic sinus surgery

Yoshiro Kai[1,2], Masanori Yoshikawa[2], Masayuki Matsuda[1], Atsuhiko Fukuoka[3], Yukio Fujita[2], Motoo Yamauchi[2] & Shigeo Muro[2]

[1]Department of Respiratory Medicine, Minami-Nara General Medical Center, Nara, Japan.
[2]Department of Respiratory Medicine, Nara Medical University, Nara, Japan.
[3]Department of Internal Medicine, Yoshino Hospital, Nara, Japan.

Keywords
Asthma, dupilumab, IL-4, IL-13, rhinosinusitis.

Correspondence
Yoshiro Kai, Department of Respiratory Medicine, Minami-Nara General Medical Center, 8-1 Fukugami, Oyodo-cho, Yoshino-gun, Nara 638-8551, Japan. E-mail: y-kai@eco.ocn.ne.jp

Received: 14 December 2020; Revised: 22 May 2021; Accepted: 3 June 2021; Associate Editor: Fu-Qiang Wen.

***Respirology Case Reports*, 9 (8), 2021, e00804**

doi: 10.1002/rcr2.804

Abstract

Dupilumab, a human monoclonal antibody against interleukin-4 (IL-4) and IL-13, has been approved for treating severe asthma and eosinophilic chronic rhinosinusitis (ECRS). Patients with ECRS are often candidates for endoscopic sinus surgery (ESS). However, a considerable number of patients have recurrent ECRS. ECRS is an important factor influencing asthma control. Here, we present two cases of severe asthma and recurrent ECRS after ESS. Although they had been treated with inhaled corticosteroids and a long-acting β2-agonist, they experienced frequent asthma exacerbations. Laboratory examinations revealed increased serum eosinophils and immunoglobulin E (IgE). Furthermore, the Asthma Control Test (ACT) score and forced expiratory volume in 1 sec (FEV_1) were indicative of airway obstruction. After treatment with dupilumab, asthma, rhinosinusitis symptoms, and pulmonary function improved remarkably. Dupilumab therapy improved quality of life in these patients with severe asthma and ECRS.

Introduction

Severe asthma is defined as asthma that remains uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS), long-acting β2-agonists (LABA), and leukotriene receptor antagonists (LTRA). Asthma is characterized by airway inflammation with variable recurring symptoms and airflow obstruction. Severe asthma is comorbid with eosinophilic chronic rhinosinusitis (ECRS). About 41.6% of patients with ECRS have asthma [1]. ECRS is a bilateral refractory chronic rhinosinusitis with polyps, predominantly affecting the ethmoid sinuses and accompanied by eosinophilic infiltration [2]. ECRS is an important factor influencing asthma control. In ECRS, clearance of the sinonasal passage is often required, and repeated endoscopic sinus surgery (ESS) is often indicated to prevent recurrence [3]. Dupilumab is an anti-interleukin-4 (IL-4) receptor α monoclonal antibody that blocks IL-4 and IL-13 signalling and is approved for atopic dermatitis, severe asthma, and ECRS with nasal polyps. In clinical trials, it significantly reduced severe asthma exacerbation, improved lung function, and controlled asthma symptoms [4]. We present two cases of asthma complicated by recurrent ECRS after ESS, whose asthma symptoms and sinusitis were rapidly improved by dupilumab.

Case Report

Case 1

A 77-year-old man with a history of ECRS was surgically treated nine years ago. In the last five years, he had been diagnosed with asthma and ECRS relapse. He was on medium-dose ICS/LABA and LTRA. His asthma and ECRS gradually deteriorated. He experienced exertional dyspnoea, continuous nasal congestion, and loss of smell. He was referred to our hospital because of his poorly

controlled severe asthma and ECRS. His Asthma Control Test (ACT) result was 13. The total serum immunoglobulin (Ig)E level was 178 IU/mL (0–148 IU/mL). Inflammatory markers indicated high peripheral blood eosinophilia (1016/μL) and elevated fractional exhaled nitric oxide (FeNO, 45 ppb). Pulmonary function (% predicted) showed a forced expiratory volume in 1 sec (FEV_1) of 1120 mL (41.9%) and FEV_1/forced vital capacity (FVC) of 33.3%. Computed tomography (CT) revealed bronchial wall thickening in the left lower lobe (Fig. 1A) and dominant ethmoid sinus shadows (Fig. 1B). His treatment was revised to high-dose ICS/LABA (1280/36 μg/day budesonide/formoterol). However, his symptoms did not significantly improve. He was then administered dupilumab (600 mg initial dose, then 300 mg every two weeks) subcutaneously. Four weeks after initiating dupilumab, his peripheral blood eosinophil count decreased from 1016 to 583/μL, and serum IgE level decreased from 178 to 128 IU/mL. His airway and nasal symptoms, including dyspnoea on exertion, nasal obstruction, and loss of smell, improved remarkably. After four weeks of dupilumab therapy, his ACT improved from 13 to 21, whereas the FEV_1 (%FEV_1) increased from 1120 (41.9%) to 1390 mL (52.0%). Furthermore, his FEV_1/FVC increased from 33.3% to 36.5% (Table 1). After eight weeks of dupilumab therapy, CT showed reduced mucus secretion in the paranasal sinus (Fig. 1C), and the patient did not experience asthma exacerbation or adverse events.

Case 2

A 54-year-old woman who never smoked had a 40-year history of severe asthma. Seventeen years ago, she underwent surgery of the small intestine due to eosinophilic gastroenteritis-induced perforation. Consequently, prednisone 40 mg was administered to treat eosinophilic gastroenteritis and continued at a 5-mg maintenance dose. Within the last four years, she was diagnosed with ECRS relapse, and her symptoms deteriorated with increasing

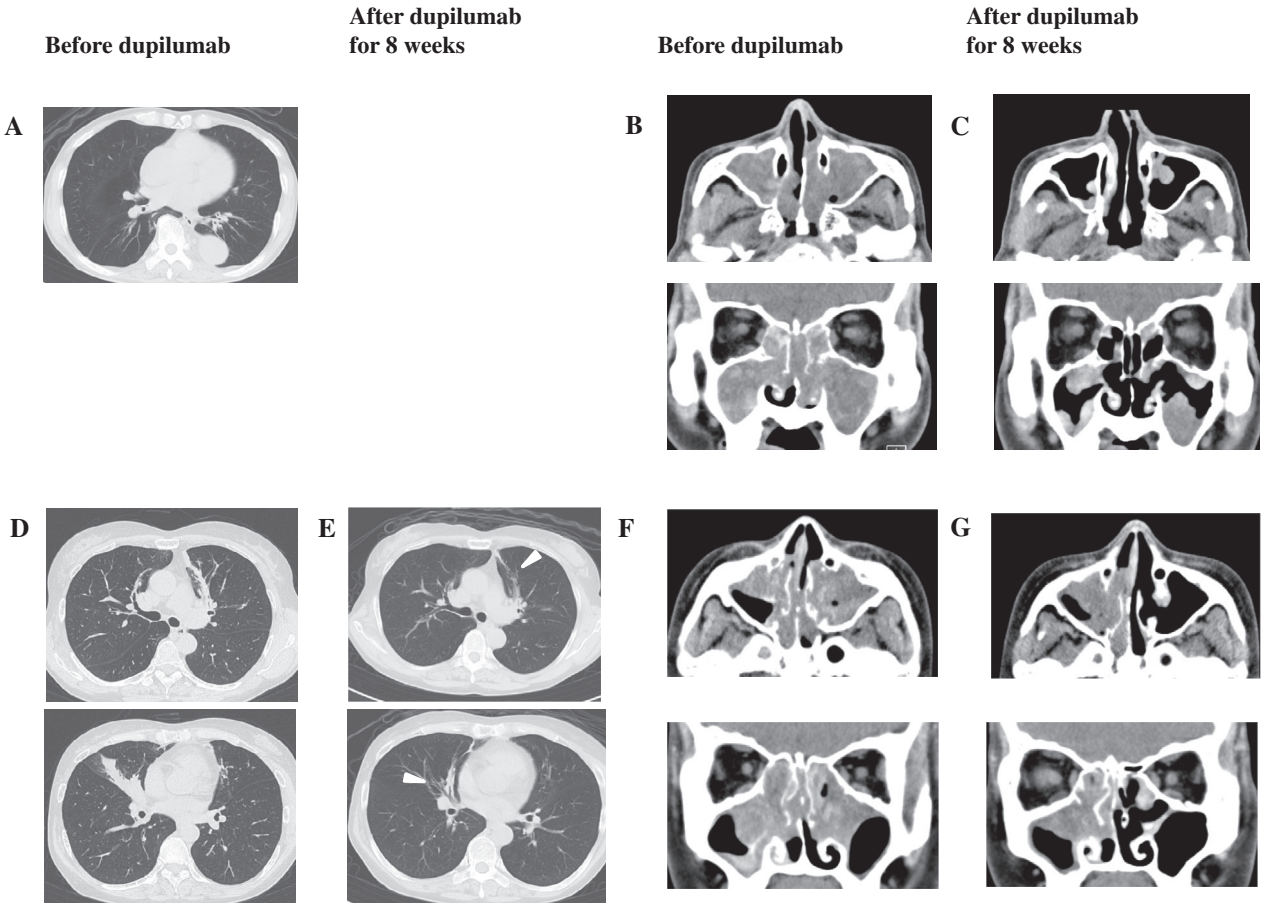

Figure 1. Chest computed tomography (CT) shows bronchial wall thickening in the left lower lobe (A). CT scans of the paranasal sinus before (B) and after (C) eight weeks of dupilumab treatment in case 1. Chest and paranasal CT scans before (D, F) and after (E, G) eight weeks of dupilumab treatment in case 2. Mucus secretion in the bronchi of the left upper and right middle lobes disappeared (E) (white arrows).

Table 1. Time course of dupilumab treatment.

	Before dupilumab therapy	After dupilumab therapy for four weeks	After dupilumab therapy for eight weeks
Case 1			
FEV_1 (mL)	1120	1390	1280
$\%FEV_1$ (%)	41.9	52.0	47.9
FEV_1/FVC (%)	33.3	36.5	34.8
FeNO (ppb)	45	18	8
Eosinophils (cells/μL)	1016	583	408
IgE (U/L)	178	128	104
ACT	13	21	21
Case 2			
OCS (mg/day)	7	5	5
FEV_1 (mL)	990	2060	2301
$\%FEV_1$ (%)	42.1	87.6	98.2
FEV_1/FVC (%)	50.25	63.4	67.7
FeNO (ppb)	20	19	16
Eosinophils (cells/μL)	849	276	345
IgE (U/L)	1470	1260	969
ACT	11	21	24

Improvement in lung function, fewer FeNO, peripheral eosinophils and IgE, and reduced symptoms were observed after treatment with dupilumab.

ACT, Asthma Control Test; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; Ig, immunoglobulin; OCS, oral corticosteroid.

dyspnoea, productive cough, nocturnal symptoms, continuous nasal congestion, and loss of smell. She had been on high-dose ICS/LABA and LTRA. Oral corticosteroid (OCS), that is, prednisone, was then increased from 5 to 7 mg. Her ACT result was 11 and serum total IgE was 1470 IU/mL. The inflammatory marker, FeNO, was normal (20 ppb); however, she had high peripheral blood eosinophilia (849/μL) despite OCS treatment. Specifically, OCS improved her bronchial inflammatory marker, FeNO; however, because of the involvement of systemic eosinophilic inflammation such as eosinophilic gastroenteritis, her peripheral blood eosinophilia did not reach normal levels. Pulmonary function (% predicted) showed an FEV_1 of 990 mL (50.3%) and FEV_1/FVC of 42.1%. CT revealed mucus secretion in the bronchi of the left upper and right middle lobes (Fig. 1D) and dominant ethmoid sinus shadows (Fig. 1F). Her treatment was changed to high-dose ICS/LABA (200/25 μg/day fluticasone/vilanterol). However, her symptoms did not significantly improve. She was treated with dupilumab (600 mg initial dose, then 300 mg every two weeks) subcutaneously. Four weeks after initiating dupilumab, her peripheral blood eosinophil count decreased from 849 to 276/μL, and the serum IgE level decreased from 1470 to 1260 IU/mL. Her airway and nasal symptoms, including dyspnoea on exertion, nasal obstruction, and loss of smell, improved remarkably. Her ACT improved from 11 at baseline to 21. The FEV_1 (% FEV_1) increased from 990 (50.3%) to 2060 mL (63.4%). The FEV_1/FVC increased from 42.1% to 87.6% (Table 1). At eight weeks, CT showed reduced mucus secretion in the bronchi and paranasal sinus (Fig. 1E, G), and she did not experience asthma exacerbation or adverse events.

Discussion

We report two cases of severe asthma with refractory ECRS, successfully treated with dupilumab. Dupilumab, an IL-4Rα antibody that inhibits IL-4 and IL-13 signalling, exhibited excellent and rapid clinical effects against both severe asthma and ECRS following two weeks of administration. IL-4 and IL-13 are key cytokines associated with type 2 inflammation in asthma. IL-4 is essential for the differentiation of naïve T helper 0 (Th0) to Th2 cells. Th2 cells induce the production of Th2 cytokines (Il-4, IL-5, and IL-13) and chemokines [eotaxin and regulated upon activation, normal T-cell expressed and secreted (RANTES)], which induce eosinophil recruitment. IL-4 induces the activation of IgE-producing plasma cells [5]. ECRS with polyps is a type 2 inflammatory disease. Asthma comorbid with ECRS was associated with a higher frequency of asthma exacerbation and reduced health-related quality of life (HRQoL) [6]. Type 2 cytokines, including IL-4, IL-5, and IL-13, are key drivers in the pathogenesis

of ECRS. In the LIBERTY ASTHMA QUEST study, higher baseline levels of serum eosinophils and FeNO are predictors of the expected response to dupilumab [4]. Dupilumab reduces severe asthma exacerbation and improves lung function [4]. Furthermore, in that study, dupilumab as an adjunct therapy significantly reduced the use of oral glucocorticoids and decreased the rate of severe exacerbations while increasing lung function (FEV_1) in patients with glucocorticoid-dependent severe asthma [7]. Dupilumab improved ECRS and asthma-related symptoms, lung function, and exercise tolerance. CT revealed a reduction in mucus secretion in the bronchus following eight weeks of treatment. Airway eosinophils and mucus contribute largely to airway obstruction associated with an upregulated IL-4/IL-13 pathway [8]. We report two cases of severe asthma with recurrent ECRS after ESS effectively treated with dupilumab. Interestingly, in case 2, a significant improvement in respiratory function was observed. The patient had allergic bronchopulmonary aspergillosis (ABPA) as a complication; this was diagnosed based on the International Society of Human and Animal Mycology criteria. ABPA was characterized by eosinophilia, elevated serum IgE levels, positive aspergillus-specific IgE, bronchial mucus plugs, and infiltrative shadows in the lungs. The significant improvement in respiratory function following treatment with dupilumab was associated with ABPA amelioration. Dupilumab may be effective in severe asthma combined with ECRS and ABPA. Dupilumab was efficacious in these patients, and it improved symptoms in comorbidities of both the upper and lower airways. Further studies are required to explore the general and specific roles of dupilumab in the treatment of severe asthma and recurrent ECRS.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Acknowledgment

We would like to thank Editage (www.editage.com) for English language editing.

Author Contribution Statement

Yoshiro Kai wrote the manuscript. All authors contributed to editing the manuscript and approved the final version of the manuscript.

References

1. Tokunaga T, Sakashita M, Haruna T, et al. 2015. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. Allergy 70:995–1003.
2. Shah SA, Ishinaga H, and Takeuchi K. 2016. Pathogenesis of eosinophilic chronic rhinosinusitis. J. Inflamm. (Lond.) 13:11.
3. Fujieda S, Imoto Y, Kato Y, et al. 2019. Eosinophilic chronic rhinosinusitis. Allergol. Int. 68:403–412.
4. Castro M, Corren J, Pavord ID, et al. 2018. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N. Engl. J. Med. 378:2486–2496.
5. Robinson D, Humbert M, Buhl R, et al. 2017. Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. Clin. Exp. Allergy 47: 161–175.
6. Denlinger LC, Phillips BR, Ramratnam S, et al. 2017. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am. J. Respir. Crit. Care Med. 195:302–313.
7. Rabe KF, Nair P, Brusselle G, et al. 2018. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N. Engl. J. Med. 378:2475–2485.
8. Svenningsen S, Haider E, Boylan C, et al. 2019. CT and functional MRI to evaluate airway mucus in severe asthma. Chest 155:1178–1189.