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DIFFERENT RESPONSES TO DUPILUMAB ON EOSINOPHILIC ASTHMA WITH CHRONIC RHINOSINUSITIS AFTER TWO CONSECUTIVE ANTI-IL-5 BIOLOGICS THERAPY FOR EACH 2-YEAR

Motohiro Kurosawa[*1a], Kumi Ogawa[1b], Yuji Shimizu[2], Yujin Sutoh[1c], and **Eijin Sutoh[1a,c]**

[1a]Department of Allergy and Respiratory Medicine, Sutoh Hospital, Annaka, Gunma, Japan.
[1b]Department of Radiology, Sutoh Hospital, Annaka, Gunma, Japan.
[1c]Department of Surgery, Sutoh Hospital, Annaka, Gunma, Japan
[2]Divison of Respiratory Medicine, Kaminakai Family Clinic, Takasaki, Gunma, Japan.

***Corresponding Author: Motohiro Kurosawa**

Department of Allergy and Respiratory Medicine, Sutoh Hospital, Annaka, Gunma, Japan.

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ABSTRACT

Objective: To investigate an efficacy of dupilumab in 4 patients of bronchial asthma with chronic rhinosinusitis (CRS) after 2 consequtive anti-IL-5 biologics therapy for each 2-year. **Methods:** The diagnostic evidence of CRS was defined using the Lund-Mackay CT score. Outcome measures involved this score as well as the Sino-Nasal Outcome Test-22 (SNOT-22) score, Question 21/22 from the SNOT-22, pulmonary function, and perpheral blood eosinophil count. **Results:** The first patient, a 54-year-old man, was given dupilumab on August 2020. Eosinophil count, FEV_1 (%), the ACT score was 101 cells/μL, 76.0 %, 24. On August 2022, eosinophil count increased, but the Lund-Mackay, the SNOT-22, Question 21/22 score decreased. The second patient, a 45-year-old woman, diagnosed with aspirin-exacerbated respiratory disease (AERD), started dupilumab on August 2020. The Lund-Mackay, the SNOT-22, Question 21/22 score was 15, 22, 5, 3. On August 2022, all of the Lund-Mackay, the SNOT-22, Question 21/22 score decreased. The third patient, diagnosed with AERD, started dupilumab on September 2020. Eosinophil count, FEV_1 (%), the ACT score was 75 cells/μL, 74.4 %, 25. The Lund-Mackay, SNOT-22, Question 21/22 score was 5, 41, 5, 3. On August 2022, eosinophil count increased, and FEV_1 (%), the ACT score decreased. The Lund-Mackay, the SNOT-22 score decreased, but Question 21/22 remained at the same. The fourth patient, a 32-year-old man, started dupilumab on April 2022. On July 2022, manifestations of CRS was improved, but eosinophil count increased. Sputum induction showed eosinophilia. Dupilumab was stopped, and he was given oral prednisone with a remarkable symptomatic improvement.

KEYWORDS: Asthma Control Test, blood eosinophil count, forced expiratory volume in 1 second, Lund-Mackay score, Sino-Nasal Outcome Test-22.

INTRODUCTION

The efficacy and safety of dupilumab, a monoclonal antibody which blocks the shared receptor subunit for interleukin (IL)-4/IL-13, has been established in patients with moderate to severe atopic dermatitis[1], moderate to severe bronchial asthma[2], and severe chronic rhinosinusitis (CRS) with nasal polyps.[3] A recent report indicated dupilumab may potentially provide a simultaneous beneficial teatment for these 3 diseases.[4] Dupilumab has been shown to improve asthma and sinonasal outcomes in adults with moderate to severe atopic dermatitis.[5] On the other hand, a real-life evaluation raised concerns anti-IL-5/IL-5-receptor has modest effects on asthma with CRS, and patients often switch between biologics.[6] An efficacy of dupilumab in patients with eosinophilic asthma with CRS has not fully been evaluated. Here we report 4 patients of eosinophilic asthma with CRS treated with dupilumab after 2 consequtive anti-IL-5 biologics therapy for each 2-year.

MATERIALS AND METHODS

The diagnosis of bronchial asthma was confirmed using the Global Initiative for Asthma (GINA) guidelines.[7] All patients met the criteria for a diagnosis of refractory asthma[8], who had been treated with daily use of inhaled corticosteroid at high dosage/long-acting ß$_2$ agonist inhalers and an additional controller for 12 months before the enrollment. The diagnostic guidelines established by the American Academy of Otorhinolaryngology-Head and Neck Surgery were met in each patient for the diagnosis of CRS.[9] All patients diagnosed the presence of nasal polyps using a nasal endoscope by experienced otolaryngologists at other hospitals before the treatment. Peripheral blood eosinophils were counted automatically by the Beckman

Coulter counter (Beckman Coulter, Fullerton, CA, USA) and MAXM A/L system (Beckman Coulter). Serum level of total immunoglobulin (Ig) E and specific IgE was measured using the CAP system (Phadia, Uppsala, Sweden). Antineutrophil myeloperoxidase antibodies were measured by an enzyme-linked immunosorbent assay analysis (Orgentec Diagnostika GmbH, Mainz, Germany). The Asthma Control Test (ACT) score[10], a forced expiratory volume in 1 second (FEV_1) and drug safety were assessed at each visit; fractional exhaled nitric oxide was not assessed, because no significant differences were found in the DREAM trial.[11] FEV_1 values were reported as a percentage of predicted values, using a spirometer (FUKUDA-77, Fukuda Denshi, Tokyo, Japan), and the best of 3 expiratory maneuvers was recorded. The Sino-Nasal Outcome Test (SNOT-22)[12] is a modification of a pre-existing instrument the SNOT-20[13] with additional 2 questions anosmia (Question 21) and nasal congestion (Question 22). Each subject completed the SNOT-22 by answering all questions at baseline, each time when a biologic switched, and after 2-year treatment with dupilumab (except case 4). Each patient had undergone a pretreatment computed tomography (CT) scan of paranasal sinuses, and diagnostic evidence of CRS was defined by the experienced radiologist using the Lund-Mackay CT score.[14] The findings of CT scan opacification were blindly staged at baseline, each time when a biologic switched, and after 2-year treatment with dupilumab (except case 4). Each biologic was administered subcutaneously according to the manufacturer's instructions, approved by US Food Drug Administration (FDA) and and European Medicines Agency (EMA).

This study was performed in accordance with Good Clinical Practice guidelines and the ethics principles outlined in the Declaration of Helsinki 2008, and approved by the Institutional Ethics Committee of Sutoh Hospital (IRB#20160055). Written informed consent was obtained from each patient before the study commenced.

RESULTS

Case 1 [Figure 1_A, 2_A]

A 54-year-old man started asthma symptoms at age 34. He was diagnosed CRS with nasal polyps by an experienced otolaryngologist. He visited our hospital on January, 2016. He was allergic asthma, diagnosed with serum total IgE level (2236 IU/mL) and positive results of specific IgE for common inhaled allergens, including *Dermatophagoides farinae* and *pteronyssinus*. His regimen included daily use of budesonide/formoterol 160μg/4.5μg inhaler and prednisone orally. On June 11, 2016, blood eosinophil count, FEV_1 of the predicted value, the ACT score, and total IgE was 312 cells/μL, 72.8 %, 22, and 1974 IU/mL. He underwent a CT scan of paranasal-sinuses, and the diagnostic evidence of CRS was defined by a radiologist at our hospital using the Lund-Mackay score, that was 19. The SNOT-22, Question 21/22 score from the SNOT-22 was 35, 5, 2. Mepolizumab was administered on the day, following withdrawal from oral prednisone on January, 2017. On July 10, 2018, blood eosinophil count decreased (73 cells/μL), percentage of predicted FEV_1 increased (78.4 %), and the ACT score was 25. Total IgE was 1938 IU/mL, and the Lund-Mackay score was 18. The SNOT-22 score decreased to 26, but Question 21/22 score remained the same. He changed to be given benralizumab. On September 5, 2020, blood eosinophil count, FEV_1, the ACT score, and total IgE was 100 cells/μL, 76.0%, 24, and 1813 IU/mL. The Lund-Mackay score decreased to 11, but the SNOT-22, Question 21/22 score remained the same. He switched to be given dupilumab. Blood eosinophil count increased, peaking at 1079 cells/μL, and decreased (901 cells/μL) on August 12, 2022. Total IgE was 928 IU/mL. The Lund-Mackay was 5, and the SNOT-22, Question 21/22 score decreased (2, 0, 1).

Case 2 [Figure 1_B, 2_B]

A 45-year-old woman started asthma symptoms at age 23. She was diagnosed with CRS, and had sinonasal surgeries for nasal polyposis at a university hospital in Tokyo. At age of 31, she was diagnosed with aspirin-exacerbated respiratory disease (AERD) by the author as described.[15] She visited our hospital on January, 2016. She was non-allergic asthma, diagnosed with total IgE 37 IU/mL and negative results of specific IgE. Her regimen included daily use of budesonide/formoterol 160μg/4.5μg inhaler and montelukast orally. On June 19, 2016, blood eosinophil count, FEV_1, and the ACT score was 443 cells/μL, 73.2 %, and 24. She underwent a CT scan of paranasal-sinuses. The diagnostic evidence of CRS was defined by a radiologist at our hospital using the Lund-Mackay score, that was 14. The SNOT-22, Question 21/22 score was 27, 5 and 2. Mepolizumab was administered on the day. On July 23, 2018, blood eosinophil count decreased (27 cells/μL), FEV_1 increased (77.9 %), and the ACT score was 25. The Lund-Mackay score, and the SNOT-22, Question 21/22 score remained the same. She changed to be given benralizumab. On September 15, 2020, blood eosinophil count, FEV_1, and the ACT score was 11 cells/μL, 73.9 %, and 24. The Lund-Mackay score, the SNOT-22, Question 21/22 score remained the same. She switched to be given dupilumab. Blood eosinophil count was increased, peaking at 347 cells/μL, and decreased to 79 cells/μL on August 16, 2022. The Lund-Mackay score was 2, and all of the SNOT-22, Question 21/22 score decreased to 0.

Case 3 [Figure 1_C, 2_C]

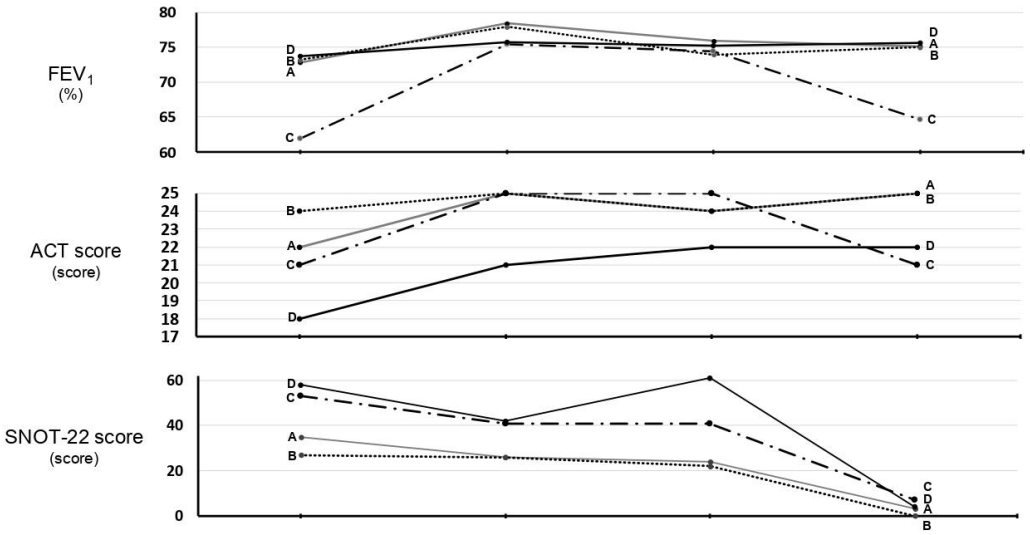
A 63-year-old man started developing asthma symptoms at age 49. He visited a university hospital in Tokyo. He was diagnosed with bronchial asthma and CRS with nasal polyps. At age of 58, he was diagnosed with AERD as described.[15] He visited our hospital on January 2016. He was non-allergic asthma, diagnosed with total IgE 117 IU/mL and negative results of specific IgE. His regimen included daily use of budesonide/formoterol

160μg/4.5μg inhaler and prednisone orally. On June 16, 2016, blood eosinophil count, FEV_1, and the ACT score was 493 cells/μL, 61.9 %, and 21. He underwent a CT scan of paranasal-sinuses, and the diagnostic evidence of CRS was defined by a radiologist at our hospital using the Lund-Mackay score, that was 11. The SNOT-22, Question 21/22 score was 53, 5, 4. Mepolizumab administration started on the day, following withdrawal from oral prednisone on January, 2017. On July 12, 2018, blood eosinophil count decreased (71 cells/μL), FEV_1 increased (75.4 %), and the ACT score was 25. The Lund-Mackay score was 8. The SNOT-22 score decreased to 41, but Question 21/22 score remained almost the same. He changed to be given benralizumab. On September 4, 2020, blood eosinophil count, FEV_1, and the ACT score was 75 cells/μL, 74.4 %, and 25. The Lund-Mackay score was 5, and the SNOT-22/Question 21 score remained the same. He switched to be given dupilumab. Blood eosinophil count was increased, peaking at 1905 cells/μL, and decreased to 585 cells/μL on August 12, 2022. FEV_1 dereased (64.6%), and the ACT score was 21. The Lund-Mackay score became 2. The SNOT-22 decreased to 8, but Question 21/22 score was 4, 2. The patient did not bother about respiratory symptoms, and because of improvements of sinonasal symptoms, he wished to keep the treatment.

Case 4 [Figure 1_D, 2_D]

A 32-year-old man started developing asthma symptoms at age 19. At age of 25, he was diagnosed with bronchial asthma at the clinic. Because of unstable respirarory symptomms, he was occasionally given systemic corticosteroids. On January, 2018, he was admitted to our hospital by an experienced pulmonologist. He was non-allergic asthma, diagnosed with total IgE 96 IU/mL and negative results of specific IgE. His regimen included daily use of budesonide/formoterol 160μg/4.5μg inhaler and prednisone orally. On April 20, 2018, blood eosinophil count, FEV_1, and the ACT score was 874 cells/μL, 73.7 %, and 18. He underwent a CT scan of paranasal-sinuses, and the diagnostic evidence of CRS was defined by a radiologist at our hospital using the Lund-Mackay score, that was 20. The SNOT-22, Question 21/22 score was 58, 5, 5. Mepolizumab was administered, following withdrawal from oral prednisone on December, 2018. On April 24, 2020, blood eosinophil count decreased (158 cells/μL), FEV_1 was 75.7 %, and the ACT score was 21. The Lund-Mackay score was 16. The SNOT-22, Question 21/22 score was 42, 4, 3. He changed to be given benralizumab. On April 22, 2022, blood eosinophil count, FEV_1, the ACT score was 122 cells/μL, 75.2 %, 22. The Lund-Mackay score increased to 20. The SNOT-22, Question 21/22 score was 61, 5, 5. He switched to dupilumab. On July 8, blood eosinophil count was increased (1755 cells/μL). The Lund-Mackay score, SNOT-22, Question 21/22 score decreased (4, 4, 0, 0). Despite a stable pulmonary function (FEV_1 75.6%, ACT score 22), he reported an increasing pruductive cough. Chest CT scan revealed no consolidations. Serum antineutrophil myeloperoxidase antibodies was not detected. Stool microscopy did not identify any ova, cysts or parasites, and serum antibody tests for the parasites *Fasciola hepatica*, *Strongyloides* spp., *Trichinella* spp., *Taenia solium*, *Schistosoma mansoni* and *Toxocara canis* were negative. Specific IgE antibodies to *Aspergillus fumigatus* and *Candida albicans* was negative. Endoscopic examinations and whole-body CT scan examinations was normal, and blood tests for tumor markers was negative. Sputum induction showed sputum eosinophilis of 30%. A diagnosis of eosinophilic bronchitis was made on the bais of the presence of excessive sputum eosinophilia. Dupilimab was stopped, and he was started on oral prednisone 30mg daily with a remarkable symptomatic improvement. On August 17, peripheral blood eosinophil count decreased (150 cells/μL) with oral prednisone 5mg daily.

Figure Legends



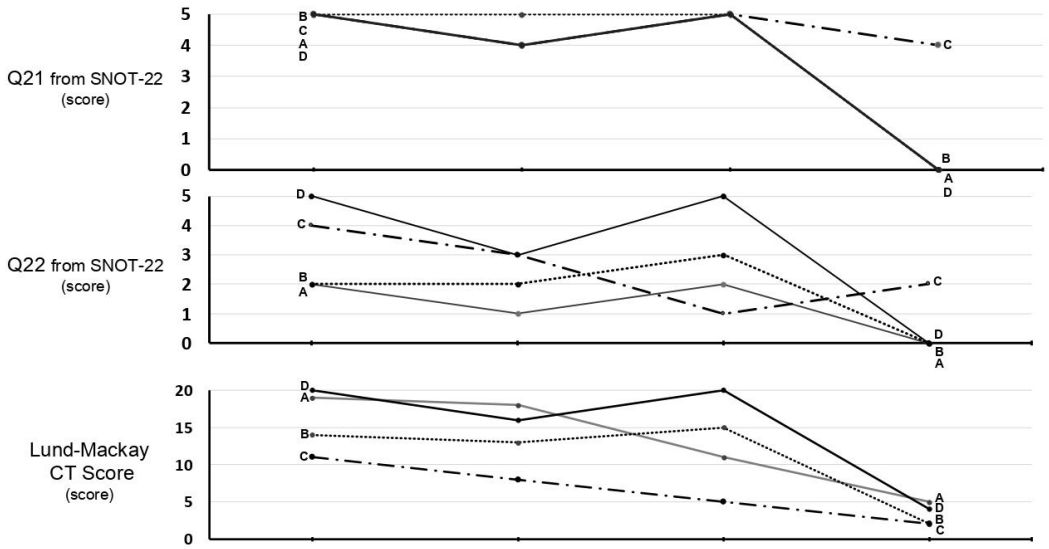


Figure 1: Change of asthma conditions and manifestations of chronic rhinosinusitis in 4 patients with the treatments (A: case 1; B: case 2; C: case 3; D: case 4). ACT, The Asthma Control Test; CT, computed tomography; FEV1, forced expiratory volume in 1 second (% predicted); Q, question; SNOT-22, The Sino-Nasal Outcome Test-22; pre-dupilumab, before dupilumab therapy; post-dupilumab, after 2-year dupilumab therapy (except case 4).

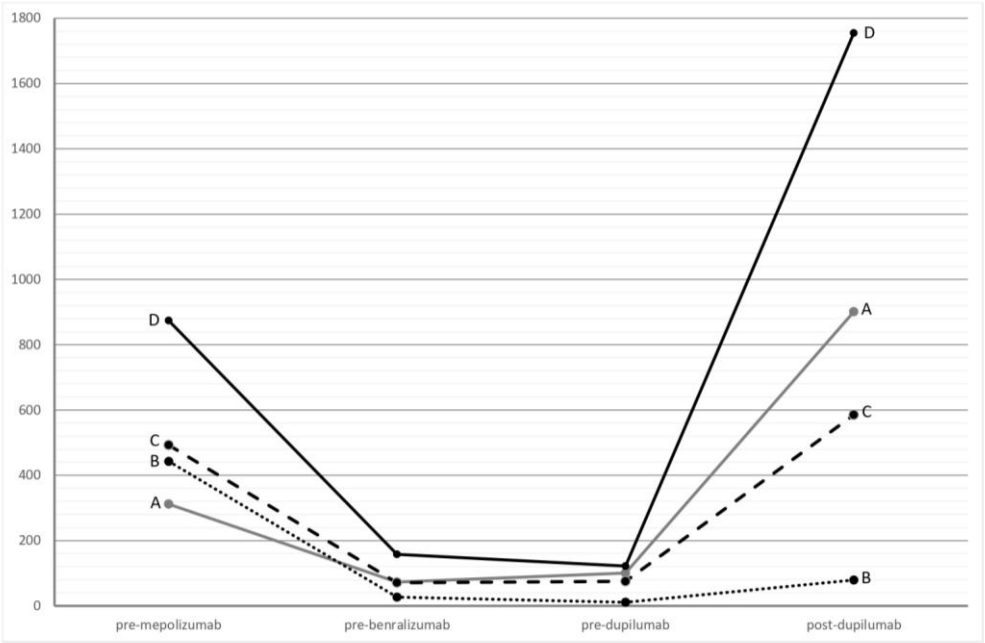


Figure 2: Change of peripheral blood eosinophil count in 4 patients with the treatments (A: case 1; B: case 2; C: case 3; D: case 4).

DISCUSSION

The exact mechanisms underlying dupilumab-induced hypereosinophilia remain unclear. IL-4/IL-13 signalilng via IL-4-receptor-α results in increased secretion of chemokines, such as the C-C type chemokines including eotaxin-1, 2, 3, which bind to CCR3 on eosinophils, resulting in eosinophil migration into peripheral tissues.[16] It is currently thought that the hypereosinophilia due to dupilumab is an epiphenomenon resulting from blockage of the signaling cascade.[17] In fact, the patient (case 1) showed his clinical course corresponded to the idea, and supported an efficacy of dupilumab. On the other hand, the patient (case 4) called the idea into the question because there was evident eosinophil migration into the airways. We ruled out secondary causes of eosinophilia, including eosinophilic granulomatosis with polyangiitis, in the present case. Several cases of eosinophilic pulmonary complications of dupilumab now have reported in the literature.[18-20] Further studies are needed.

The reason why the patient (case 3), who was AERD, remained anosmia/nasal-congestion, and developed decreased pulmonary functions after switching from anti-IL-5/IL-5-receptor to dupilumab is not completely understood. On the other hand, we observed an efficacy of dupilumab in the patient with AERD (case 2), that corresponded to the report.[21]

Atopic dermatitis is a chronic inflammatory skin disease, characterized by complex pathophysiology involving skin barrier dysfunction and aberrant type 2 inflammatory/ immune response[22], and a percutaneous entry of environmental allergens through barrier-disrupted skin has been shown to elicit a type 2-dominant cytokine response.[23] Blocking IL-4 signaling in atopic dermatitis with dupilumab showed a progressive reverse of the skin[24], supporting skin barrier dysfunction is a relevant basic pathogenesis. On the other hand, the silent features of the pathology of allergic/non-allergic asthma is eosinophilic bronchitis and desquamation of the bronchial mucosa[25], summarized as chronic desquamative eosinophilic bronchitis. Eosinophilic inflammation is highly important and involved in the damage of the epithelium and submucosa, following a remodeling. Taking all into account, we may hypothesize that pathogenesis between atopic dermatitis and eosinophilic asthma may be different. So, prospective studies of respiratory biologics especially for patients with AERD would allow for further identification of the responder endotype to guide selection of appropriate biologic therapy.

CONCLUSION

We report 4 patients of eosinophilic asthma with CRS treated with dupilumab after 2 consequtive anti-IL-5 biologics therapy for each 2-year. Four of them showed different responses to dupilumab, indicating close monitoring of patients who are switched from anti-IL-5 biologics to dupilimab remains essential.

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