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Letter to the Editor

Efficacy of dupilumab and biomarkers for systemic corticosteroid naïve allergic bronchopulmonary mycosis

Dear Editor,

Allergic bronchopulmonary mycosis (ABPM) is caused by hypersensitive reaction to mycosis and worsened pulmonary function with developing airway dysfunction.¹ The clinical characteristics are featured uncontrolled asthma with elevation of blood eosinophils and total immunoglobulin E (IgE), positive findings of the mycosis specific IgE and precipitating antibodies, chest radiological findings of central bronchiectasis and consolidation, existence of mucus plug.² Systemic corticosteroid, which is pivotal treatment for acute stage of ABPM improves the pathophysiology³ however, long term corticosteroid administration causes adverse effect such as hyperglycemia, cataract, glaucoma, osteoporosis and severe infections associated with immune dysfunction.⁴ Here, we reported that beneficial effect of dupilumab, a novel biologic agent with blockade of interleukin (IL)-4 and IL-13 signals for systemic corticosteroid naïve ABPM patients and clarified CD40 ligand (CD40L) might be useful biomarker for ABPM. These data will practically contribute to future treatment strategy for patients with ABPM to avoid glucocorticoid-related adverse effects.

A 72-year-old Japanese woman who had cataract and treatment history of non-tuberculosis mycobacterium (NTM) had been treated with inhaled corticosteroid, long acting β_2 adrenergic agonist, long acting muscarinic antagonist and leukotriene receptor agonist for asthma diagnosed 5 years ago and experienced asthma exacerbations for twice in previous year. She had no history of sinusitis, smoking, dust exposure, or treatment with anti-fungal agents. On physical examination, she had productive cough and coarse crackles in both sides of chest without fever, hypoxia and skin rash. Her chest X-ray showed nodules with reticular shadows in bilateral lung fields, and chest computed tomography (CT) showed centrilobular nodules, infiltrations, and high-attenuation mucus in the bronchi with central dilatation (Fig. 1a–c). These abnormalities on CT had been worsening compared to the findings 4 years earlier. On laboratory examination, the white blood cell count was 11,600/ μ L, with 21.7% neutrophils, 25.6% lymphocytes, and 48.6% eosinophils (5637/ μ L), total IgE was 2525 IU/mL, and C-reactive protein, β -D glucan, antineutrophil cytoplasmic antibody, and other biological results were within normal ranges. *Aspergillus* and *Penicillium*-specific IgE levels were 9.55 UA/mL and 7.31 UA/mL, respectively, and precipitating antibodies for *Aspergillus* were positive. Bronchoscopy showed a mucus plug in the central bronchus, and the histopathological findings of the mucus showed infiltration of eosinophils with Charcot-Leyden crystals and mycotic

mycelia on Grocott staining. *Penicillium species* was detected in cultured specimen without other mycosis and mycobacteria. Pulmonary function testing showed forced expiratory volume in 1 s (FEV1) at 1540 mL, %FEV1.0 at 93.3% and fractional exhaled nitric oxide (FeNO) at 98 ppb. She was diagnosed as ABPM and treated dupilumab prior to systemic administration of corticosteroid considering to the related critical adverse effect including augmentation of cataract and NTM. Six weeks later, her symptoms recovered from 17 to 24 points on the asthma control test score with elevation of FEV1 to 1850 mL, and IgE decreased to 1124 IU/mL. Blood eosinophils were 43.8% (2847/ μ L) at this point. Three months after initiation of dupilumab, recovery of her symptoms was maintained, and centrilobular nodules, infiltrations, and high-attenuation mucus shadows on chest CT had disappeared (Fig. 1d–f), with significant improvement of pulmonary function, FeNO, and serum IgE (689 IU/mL), with no elevation of blood eosinophils (Supplementary Table 1). *Aspergillus* and *Penicillium*-specific IgE levels were decreased to 7.85 UA/mL and 2.46 UA/mL, respectively. Serum cytokines and chemokines were analyzed by multiplex assay (Eve Technologies, Calgary, Alberta, Canada) and ELISA (for periostin, Shino-test, Tokyo, Japan), before and after treatment of dupilumab at 3 months (Table 1). Epithelial growth factor (EGF), granulocyte macrophage colony stimulating factor (GM-CSF), interferon alpha 2 (IFN α 2), CC chemokine ligand (CCL) 22, platelet derived growth factor (PDGF)-AA, CD40L, IL-5 and periostin were decreased by treatment of dupilumab with improvement of ABPM pathophysiology.

Pivotal treatment of acute stage ABPM is systemic corticosteroid however, long-term administration is needed which induces corticosteroid related adverse effects.³ In the present case, patient had past history of cataract and NTM which had possibility to increase risk of corticosteroid-related adverse effect. Hence, she was administered dupilumab prior to systemic administration and was able to evaluate the effect of dupilumab itself for ABPM patient avoiding with corticosteroid related adverse effect, which is supported by previous report.⁵ Moreover, the present case allowed us to evaluate the biomarker for the treatment and pathophysiology of ABPM.

Dupilumab is a human monoclonal antibody targeting IL-4 receptor α , the shared subunit of the type 2 cytokines of IL-4, IL-13 and has capacity for blockade both signaling. For uncontrolled asthma patients on phase 3 randomized trial, dupilumab improved rate of exacerbation and pulmonary function with reduction of oral corticosteroid administration.⁶ The efficacy is better in patients with higher total IgE than those with lower total IgE⁶ which is regulated the production from B cells by IL-4 and IL-13. In the present case, dupilumab was selected considering the pathophysiology of

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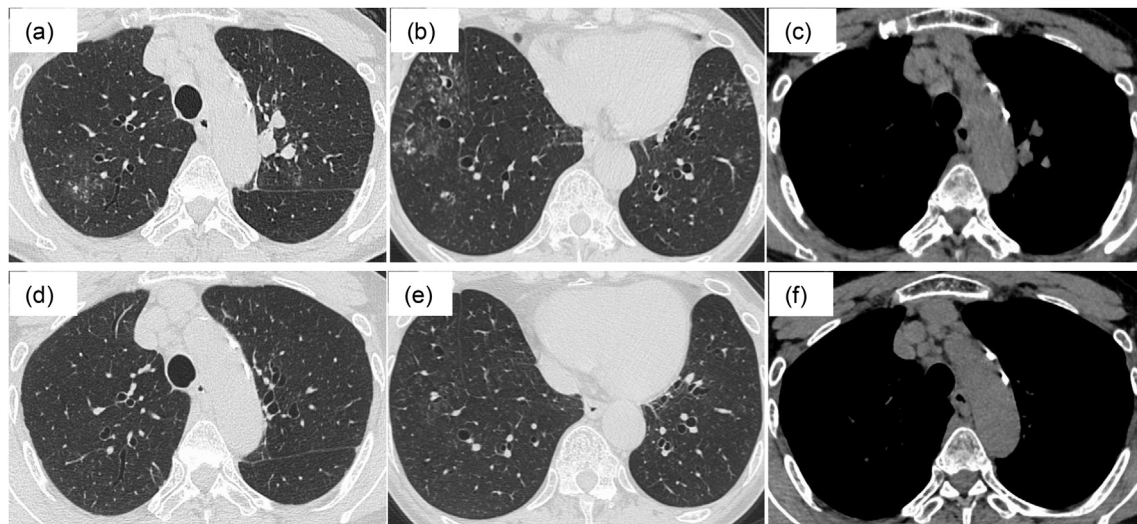


Fig. 1. Findings on chest computed tomography (CT) before treatment of dupilumab (a–c) and after treatment of dupilumab (d–f). (a,b) Chest CT of lung window shows centrilobular nodules and infiltrations with mucus plug in dilated central bronchus. (c) On mediastinal window, mucus plug shows higher attenuation than skeletal muscle. (d–f) Centrilobular nodules, infiltrations and mucus plug are disappeared after treatment of dupilumab.

Table 1

Serum cytokines and chemokines of present case before and after treatment of dupilumab.

pg/ml	Before Dupilumab	After Dupilumab
EGF	110.6	11.8
Eotaxin	26.0	42.4
TGF- α	1.8	2.2
GM-CSF	51.8	33.8
IFN α 2	27.8	N.D.
IFN γ	2.0	1.5
CXCL1	1246.3	1065.4
CCL22	1443.1	693.8
PDGF-AA	1521.4	1294.7
PDGF-BB	2501.1	2314.2
CD40L	2018.0	628.3
IL-4	N.D.	N.D.
IL-5	1.4	0.3
IL-7	1.4	2.0
IL-8	3.7	8.0
IL-13	N.D.	N.D.
CXCL10	57.7	82.5
CCL2	220.7	245.6
CCL3	2.4	2.7
CCL4	72.4	90.6
CCL5	328.7	313.9
TNF α	8.1	5.9
VEGF-A	30.5	27.1
IL-18	79	66
Periostin (ng/ml)	58	49

EGF, epithelial growth factor; TGF- α , tissue growth factor- α ; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN α 2, interferon- α 2; CXCL1, C-X-C Motif Chemokine Ligand 1; CCL22, C-C motif chemokine 22; PDGF-AA, platelet-derived growth factor-AA; CD40L, CD40 ligand; IL, interleukin; TNF α , tumor necrosis factor α ; VEGF-A, vascular endothelial growth factor-A; N.D., not detected.

ABPM, with elevation of total IgE levels in blood and augmentation of type 2 inflammation driven by fungal-specific IgE,⁷ although other biologics such as anti-IL-5 antibody have been reported as having potential clinical effectiveness for ABPM.^{8,9} Dupilumab indicated significant recovery of symptoms, pulmonary functions disappearing of mucoid impaction without administration of

corticosteroid. As the mechanisms, IL-13 dependent mucus production was attenuated via mucin (MUC)5AC and MUC5B according to previous report.¹⁰ Additionally, decline of total IgE, which is reported as biomarker of treatment efficacy for ABPM¹¹ improved clinical characteristics by attenuation of inflammatory mediators from mast cells.

It was found that cytokines and chemokines such as EGF, GM-CSF, IFN α 2, CCL22, PDGF-AA, CD40L, IL-5, and periostin in serum tended to decrease on treatment with dupilumab, which might reflect the pathophysiology of ABPM. To evaluate useful biomarkers for ABPM, we compared the cytokines and chemokines to those in 6 females, similar age patients with mild to moderate stable asthma including various phenotypes of body mass index, blood eosinophil, IgE, FeNO and pulmonary function (Supplementary Table 1, 2). IL-5, strong activator of eosinophils with increasing evidences¹² was higher in present case before treatment of dupilumab than stable asthma patients and decreased to the level of stable patients after treatment of dupilumab. Importantly, Eotaxin which associated with migration of eosinophils was elevated after treatment of dupilumab however, not reached to the level of stable asthma patients and CCL2 was also not altered by treatment of dupilumab. These data and clinical efficacy disappearing of eosinophils infiltrated mucus plug indicated that dupilumab might contribute to attenuate local eosinophilic inflammation even in continuous elevation of blood eosinophils. Additionally, dupilumab improved the clinical findings of ABPM without normalization of blood eosinophil counts, which also indicated that blood eosinophil is not a marker for the response of dupilumab treatment in ABPM. Notably, a previous report indicated the possibility of increased blood eosinophils after treatment with dupilumab.⁵ Thus, it would be necessary to perform frequent observations of blood eosinophil levels and clinical abnormalities after dupilumab treatment. Moreover, CD40L which associated with T cell activation with production of IL-4 and induction of IgE production from B cells¹³ was higher before treatment of dupilumab than stable asthma patients and significantly decreased at the lower level than stable asthma patients. The data indicated that CD40L might be an effective biomarker of ABPM pathophysiology through IL-4 and IL-13 signaling. The

immunoglobulin G (IgG)/IgE ratio reflecting B cell class switching from IgG to IgE was lower in the present case before treatment with dupilumab than in stable asthma patients, and it increased after treatment with dupilumab (Supplementary Table 1). These data suggest that a low IgG/IgE ratio in ABPM patients might be a predictor for treatment with dupilumab instead of CD40L, because that could not be tested in the clinical situation. Since the current biomarker results came from a single case, a larger study with more patients would be necessary to confirm the validity of the results.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.08.006>.

Conflict of interest

The authors have no conflict of interest to declare.

Hiroki Tashiro^{*}, Koichiro Takahashi, Yuki Kurihara,
Hironori Sadamatsu, Shinya Kimura, Naoko Sueoka-Aragane

Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan

^{*} Corresponding author. Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan.

E-mail address: si3222@cc.saga-u.ac.jp (H. Tashiro).

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