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Allergic Bronchopulmonary Aspergillosis in Identical Twins: Effectiveness of Dupilumab

Pedro A. Lamothe, MD, PhD[1,#], **Martin Runnstrom, MD**[1,#], **Natalia Smirnova, MD**[1], **Flavio C. Flores, MD**[2], **Aaron Shepherd, MD**[2], **Jiwon Park**[2], **F. Eun-Hyung Lee, MD**[1,*]

[1]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

[2]Morehouse School of Medicine, Atlanta, GA, USA

Allergic bronchopulmonary aspergillosis (ABPA) occurs from a hypersensitivity reaction to the fungus *Aspergillus* and shares some pathogenesis with asthma (1). Oral corticosteroids (OCS) are usually the initial treatment of choice, but response is variable and side effects are common. For these reasons, there is a need to identify different treatment options for ABPA. Th2 inflammation is a shared pathway for many patients with severe asthma and ABPA (1). Small studies have shown promise using biologic therapies approved for asthma to treat ABPA, but large randomized trials are lacking. Dupilumab is a human monoclonal IgG4 antibody against the IL-4 receptor alpha subunit (IL-4rα) that blocks the activity of both IL-4 and IL-13 cytokine signaling pathways (2). The use of dupilumab in ABPA has been limited to case reports and series. Our group and others have reported improvement of symptoms, reduction of exacerbations, and a decrease in OCS use with dupilumab in patients with ABPA (3–6).

Like any other complex disease, genetics is one of the variables that could play a role in the clinical manifestation and response to treatment in patients with ABPA. Here, we present a unique case of genetically identical twin sisters with severe asthma and ABPA

*Corresponding author: F. Eun-Hyung Lee MD, 615 Michael St. NE, Ste. 205, Atlanta, GA 30322, f.e.lee@emory.edu, Phone: 404-712-2970.

#These authors contributed equally to this work.

Authors' contributions

PAL and MR wrote the manuscript.

PAL, MR, AS, and JP prepared the figures.

PAL, AS and NS performed clinical data acquisition and analysis for figure preparation. NS and FCF helped with manuscript preparation and provided significant editorial input FCF obtained consent from patients for publication.

FEL conceptualized the idea of this project, provided guidance to all other authors, obtained funding for the project, and oversaw the manuscript and figure preparation.

Statement of informed consent obtained.

We obtained written informed consent from both patients in our study for publication.

Conflicts of interest

PAL, MR, NS, FCF, AS, and JP have no conflicts of interest to disclose.

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who had different clinical outcomes after only one agreed to be treated with biologics. Both twins met the Asano 2021 criteria for ABPA diagnosis (7). Their clinical characteristics are summarized in the Table E1. This table shows that before presentation, both twins had similar clinical courses, comorbidities, exposures, risk factors, and medications.

Twin 1 is a 61-year-old female with long-standing asthma presented to our clinic in 2014. She was found to have airflow limitation with a forced expiratory volume in the first second (FEV_1) of 65% of predicted, a total IgE of 496 IU/mL with a blood eosinophil count of 1340 cells/μL (Figure 1), central bronchiectasis on computed tomography (CT) of the chest (Figure E1), along with a positive Aspergillus-specific IgE and skin test. She was diagnosed with ABPA and started on daily prednisone, itraconazole, and omalizumab. Despite treatment adherence, her symptoms persisted, and she continued to have exacerbations, airflow limitation, airway inflammation, and blood Th2 biomarker elevation (Figure 1). She was then switched to mepolizumab with good response and was able to discontinue daily prednisone. However, after two years on mepolizumab, she had several exacerbations and was restarted on daily prednisone. She was then transitioned to dupilumab followed by a rapid and substantial clinical improvement. Shortly after dupilumab was started she experienced asymptomatic hypereosinophilia that self-improved over time. Almost 4 years after initiating dupilumab, she has remained free of exacerbations and has not needed regular prednisone (Figure 1). She also has minimal symptoms, normal lung function, evidence of low airway inflammation, and total serum IgE below 150 IU/mL (Figure 1) and undetectable Aspergillus-specific IgE.

Twin 2 presented to our clinic in early 2021 with long-standing eosinophilic asthma and frequent exacerbations. Due to having required repetitive courses of OCS for many years, she had developed avascular necrosis of bilateral hips requiring bilateral hip replacements. In our clinic, she was found to have airflow limitation with an FEV_1 of 58% of predicted, a peripheral blood eosinophil count of 2,350 cells/μL (off OCS), a total IgE of 842 IU/mL, and an Aspergillus-specific IgE of 18.6 IU/mL. CT of the chest showed central bronchiectasis and high attenuation mucus impaction (Figure E1). Like her twin sister, she was diagnosed with ABPA, and was started on daily OCS. However, she declined to start a biologic or antifungal therapy. One year later, she continues to require daily OCS and unfortunately has developed prediabetes.

Illustrating the role of genetics in ABPA, we compare the unique cases of twin sisters with ABPA. One twin was treated with three different biologic therapies over the course of 8 years, while the other declined biologic treatment. The debate on how much genetics and environment impact ABPA is ongoing. Interestingly, both sisters were born and raised in the Southeastern United States with similar but non-identical environmental exposures. Some fungi, especially Aspergillus, are known to be ubiquitous in this part of the world, making exposure to them essentially unavoidable. Thus, for ABPA, genetics may seem to play an important role in disease susceptibility.

In this report of two patients with genetic homogeneity, the long-term effectiveness of dupilumab to treat ABPA in Twin 1 is encouraging. Although control was not achieved with omalizumab or mepolizumab, Twin 1 is now exacerbation free with minimal symptoms for

almost 4 years on dupilumab. She has evidence of bronchiectasis due to permanent scarring from previous ABPA exacerbations, but she has no signs of current airway inflammation or mucus impaction on imaging (Figure E1), and her markers of Th2 inflammation have greatly improved.

In contrast, Twin 2 who declined biologic therapy continues to be OCS dependent despite suffering from corticosteroid related adverse effects. Her most recent CT of the chest shows cylindrical bronchiectasis with multiple areas of high-attenuation mucus impaction and tree-in-bud micronodules consistent with active airway inflammation (Figure E1).

With six different biologics FDA approved for treating severe asthma (2), one important question is whether one is superior for the management of ABPA. Both omalizumab and IL-5 targeted therapies may benefit symptoms in ABPA, but only IL-5 signaling blockade has been shown to clear mucus plugs (8). Recently, there have been two reports of favorable clinical response to dupilumab after failure of anti-IL-5 therapy (4, 6), suggesting interruption of upstream T2 mediators such as IgE may be critical to prevent exacerbations. Dupilumab may specifically benefit patients with ABPA by the following mechanisms: 1) inhibition of IL-13 that upregulates the Muc5ac gene implicated in the generation of airway mucus (9) and/or 2) reduction of IgE production by inhibition of local B cell differentiation into IgE antibody secreting cells. Dupilumab likely interrupts the initial pathogenic mechanism of IgE-mediated immune cell activation.

This study shows how genetics and environmental exposures play a role in ABPA, and the benefits of dupilumab in patients with uncontrolled ABPA.

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Clinical Implications

We describe the cases of identical twins with ABPA, but only one of them received biologic therapies. We used their genetic homogeneity as a basis for assessing the effectiveness of dupilumab in treating ABPA.

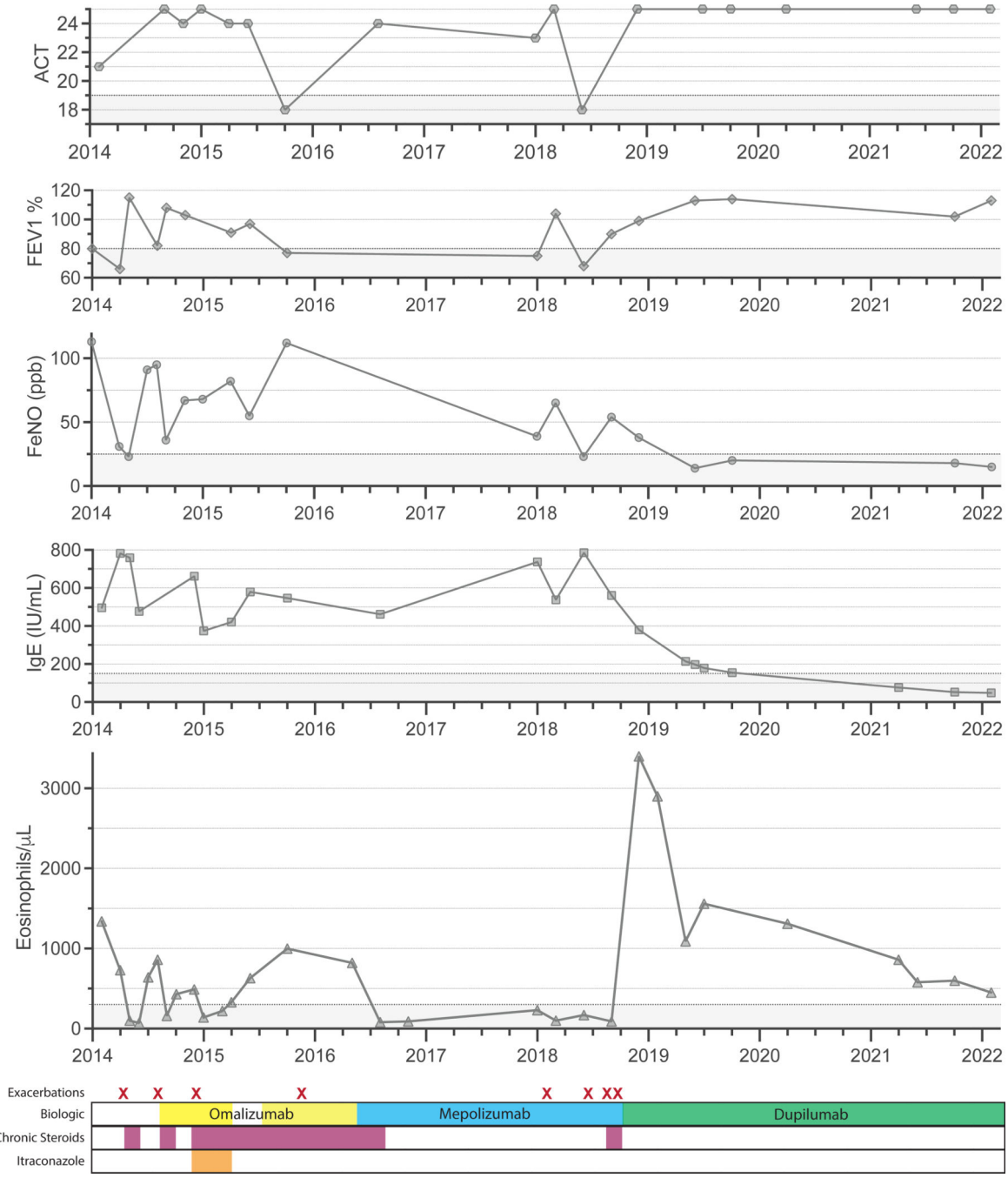
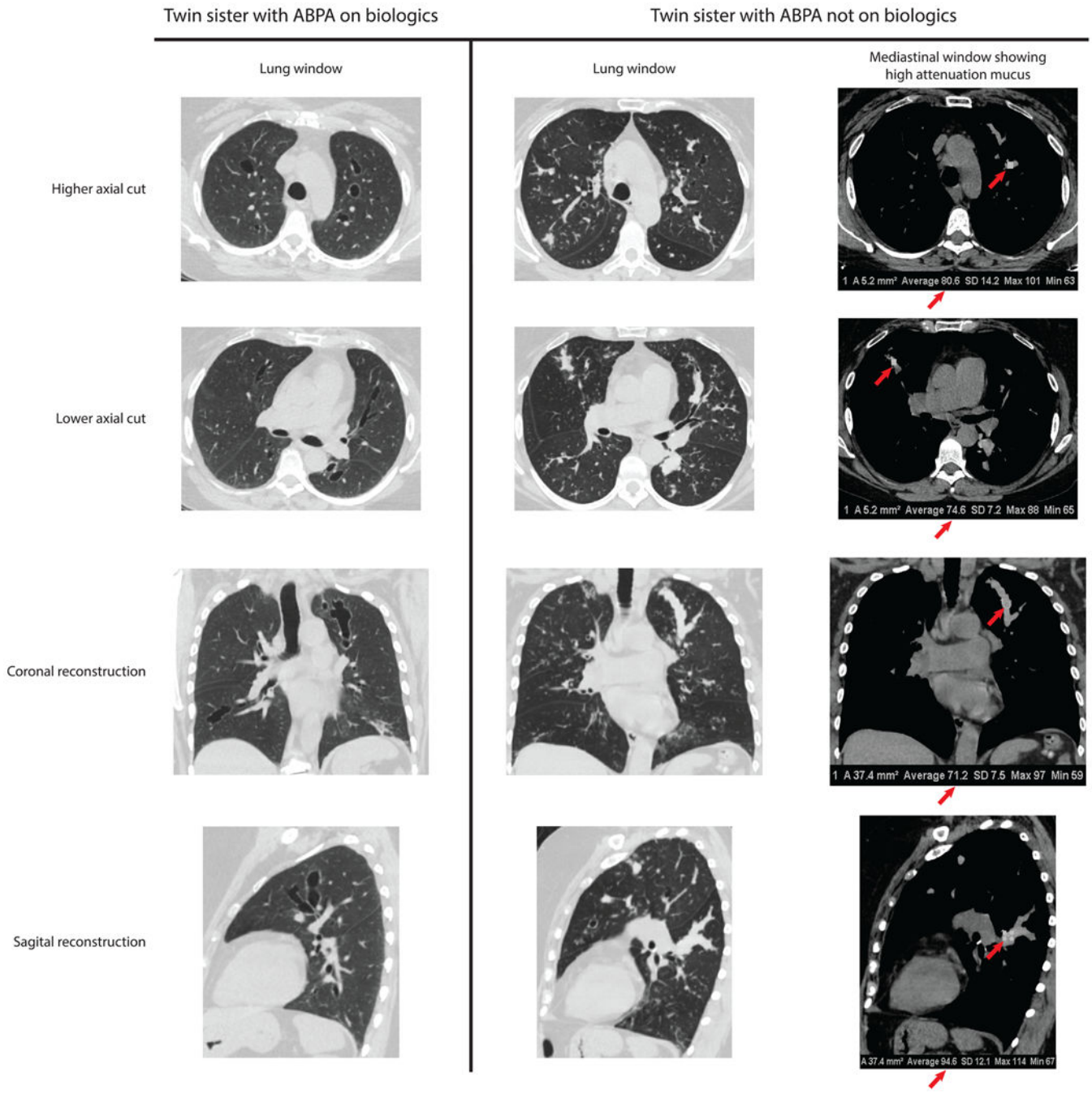


Figure 1. Clinical course of twin 1.

A) Clinical parameters from top to bottom: Asthma Control Test (ACT), forced expiratory volume in the first second (FEV_1) percent of predicted, fractional exhaled nitric oxide (FeNO), parts per billion (ppb), total immunoglobulin E (IgE) IU/mL, eosinophils/μL. B) Biologic therapy (top), daily prednisone (middle), and antifungal treatment (bottom). Exacerbations are noted with an "X".



Online repository figure E1. Chest CT findings of both patients.

A) Twin 1 on biologic therapy. Central bronchiectasis are seen without mucus impaction and without parenchymal abnormalities. B) Twin 2 not on biologic therapy. Lung windows (left) reveal central cylindrical bronchiectasis, mucus impaction, and tree-in-bud nodularity. Mediastinal windows (right) show high attenuation mucus with Hounsfield units > 70 (red arrows).

Online repository table E1:

Patients' clinical characteristics, exposures, risk factors and medications.

	TWIN 1	TWIN 2
SMOKING	Former smoker, quit in 1995, 5 pack-year smoking history. Never smoked or inhaled other products	Former smoker, quit in 1998. Never smoked or inhaled other products
COMORBIDITIES	Hypertension, hypercholesterolemia, type 2 diabetes mellitus, vitamin D deficiency, well-controlled GERD, mild allergic rhinitis, osteoarthritis	Hypertension, hypercholesterolemia, prediabetes, vitamin D deficiency, bilateral avascular necrosis of hips, colonic polyps, mild allergic rhinitis
PHYSICAL ACTIVITY	4–6 times per week, aerobics, weight training, 31–60 minutes	Walks 30 min slowly at least 5 times per week
AIRWAY CLEARANCE	Flutter valve	Unknown
INHALERS COMPLIANCE AND TECHNIQUE	Good	Good
GREW UP	Mississippi	Mississippi, Texas, Louisiana
LIVE IN	Atlanta, GA	Atlanta, GA
BMI	33.5	32
GERD OR DYSPHAGIA	GERD, well controlled with esomeprazole, no dysphagia	No
ENVIRONMENTAL EXPOSURES	None	None
WORK-RELATED EXPOSURES	None	None
EXTRAPULMONARY MANIFESTATIONS	Mild allergic rhinitis, now well controlled on dupilumab. She does not need intranasal corticosteroids anymore	Mild allergic rhinitis, controlled with intranasal corticosteroids
SIGNIFICANT TRAVEL-RELATED EXPOSURES	None	None
CURRENT MEDICATIONS	Budesonide-formoterol, albuterol, cholecalciferol, esomeprazole, hydrochlorothiazide-losartan, rosuvastatin, dupilumab	Fluticasone-vilanterol, albuterol, cholecalciferol, docusate, montelukast, triamcinolone nasal spray, hydrochlorothiazide-losartan
ASTHMA HISTORY BEFORE PRESENTATION TO OUR CLINIC	Asthma started during childhood. Well controlled from late teenage years to her early 40s. In her 40s she started with maintenance controller inhalers. In her 50s she started to have 3–4 exacerbations per year requiring corticosteroids. Never hospitalized or intubated for asthma. Intermittent use of daily prednisone 10 mg over the past several years	Had asthma during childhood but then went away at age 8. At 22 years of age her asthma symptoms presented again and started maintenance controller inhalers. She was well controlled until age 50 when she started to have 3–4 exacerbations per year requiring oral corticosteroids. Never hospitalized or intubated for asthma. Intermittent use of daily prednisone 5 to 10 mg for several years
ASTHMA MEDICATIONS USED BEFORE PRESENTATION TO OUR CLINIC (NO LONGER TAKING)	Montelukast, theophylline, fluticasone-salmeterol, mometasone-formoterol, aclidinium, cetirizine	Budesonide-formoterol, fluticasone-salmeterol
FAMILY HISTORY	Mother with asthma	Mother with asthma, daughter with asthma and eczema
WORK	Banker until 1999 and thereafter stay-at-home mother	Office manager and banker
PETS	None	None