LETTER TO THE EDITOR
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Effects of Dupilumab for Asthma-chronic Obstructive Pulmonary Disease Overlap

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Dear Editor:

In Japan, diagnostic criteria for asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) have been published by the Japanese Respiratory Society.[1] ACO involves both asthma and COPD elements, and so can be considered a phenotype of either asthma or COPD. ACO may be present in 10–40% of COPD patients and 15–35% of asthma patients,[2] with these populations showing different characteristics, prognoses, and medication requirements. ACO has been recently suggested to include two distinct phenotypes: COPD with coexistent asthma and eosinophilic COPD.[3,4] Other treatises have divided ACO into other phenotypes, such as smoking asthmatics and eosinophilic COPD.[5,6] Optimal therapeutic regimens and response to therapy in ACO remain undefined. Long-acting β_2-agonists and long-acting muscarinic antagonists in combination with inhaled corticosteroids are often used to treat ACO,[7,8] but some cases cannot be controlled by these treatments. The use of biologics for ACO remains controversial, and very few clinical trials have evaluated the efficacy of biologics therapy in ACO because ACO patients are usually excluded from clinical trials of COPD or asthma therapies. Only omalizumab and mepolizumab have been reported as effective summary of biologics with respect to ACO but included no information on dupilumab.[11]

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Dupilumab is a fully human anti-interleukin (IL)-4 receptor α (IL-4Rα) monoclonal antibody that blocks both IL-4 and IL-13 signaling because IL-4Rα is a common subunit of IL-13 and IL-4. Few reports appear to have described the use of the forced oscillation technique (FOT) to determine the effects of dupilumab on ACO.

We report herein three cases in which biologics were added and dupilumab proved effective. Effects were confirmed from subjective symptoms, lung function, fractional exhaled nitric oxide (FeNO), and the FOT. All patients were diagnosed with ACO according to the diagnostic criteria of the ACO guidelines.[1,12]

The FOT was conducted with the patient in a sitting position using a nose clip and mouthpiece with respiration at resting levels. FOT measurements are taken during resting respiration and require very little time (<1 min). The reproducibility of this method has been confirmed.[13] FOT can also measure other respiratory parameters determined by spirometry.[14] The present study used an FOT machine (MostGraph Chest Co., Tokyo, Japan) that can measure respiratory mechanics using FOT (Figure 1).

Case 1 involved a 77-year-old man with a long history of smoking (Brinkman index>600). He had been visiting our hospital for bronchial asthma and COPD for >15 years and had been using a mometasone furoate dry powder inhaler (200 μg, one inhalation once a day, Asmanex; MSD, USA), inhaled indacaterol/glycopyrronium fixed-dose combination (IND/GLY) (110/50 μg, one inhalation once a day, Ultibro; Novartis, Switzerland), and L-carbocysteine

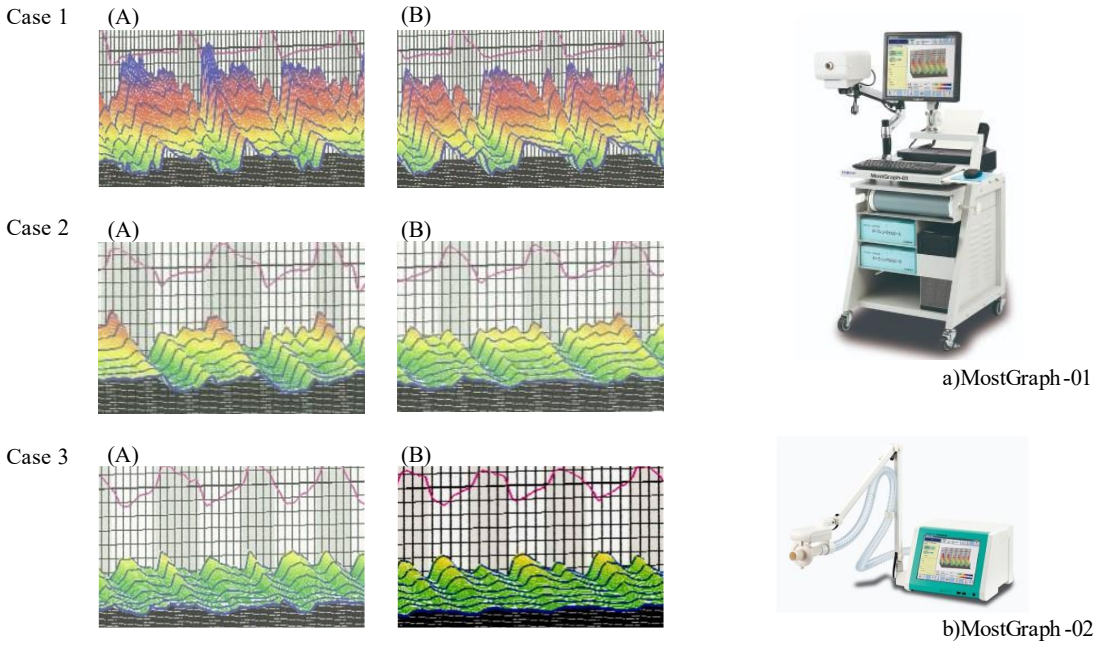

Figure 1. The forced oscillation technique (FOT) machine (MostGraph Chest Co., Tokyo, Japan).
a) MostGraph-01. b) MostGraph-02. Results of the forced oscillation technique by MostGraph in three cases. A) Color 3D imaging patterns of respiratory impedance in patients with ACO before starting dupilumab (Cases 1–3). B) Color 3D imaging patterns of respiratory impedance in patients with ACO at 6 months after starting dupilumab (Cases 1–3).

Kyorin Pharmaceutical, Japan). Long-term oxygen therapy had been introduced 3 years earlier. He had started mepolizumab (100 mg, every 4 weeks, Nucala; GSK, UK) 6 months prior, but neither lung function nor subjective symptoms improved, so mepolizumab was changed to dupilumab (loading dose of 600 mg followed by 300 mg every other week, DUPIXENT; Sanofi, France). Six months after introducing dupilumab, lung functions did not appear to improve. However, subjective symptoms such as findings from the asthma control test (ACT) and COPD assessment test (CAT) were improved, and FeNO and serum immunoglobulin (Ig) E were markedly better. In addition, improvements in respiratory resistance were seen with the FOT (Figure 1). Serum eosinophil count increased after starting dupilumab, but no adverse effects of serum eosinophilia were observed (Table 1).

Case 2 involved a 73-year-old woman with long-term effects from passive smoking. She had been visiting our hospital for bronchial asthma and COPD for 10 years and was being treated with budesonide/formoterol (160/4.5 μg, two inhalations twice daily, Symbicort; AstraZeneca, UK), tiotropium (2.5 μg, two inhalations once daily, Spiriva; Boehringer Ingelheim, Germany), montelukast (10 mg once daily, Singulair; MSD, USA), and carbocysteine (500 mg, 3 times/day, MUKODYNE; Kyorin Pharmaceutical). Since she required frequent steroid bursts and showed deteriorated lung function, subcutaneous injections of 600 mg anti-IgE antibody omalizumab (Xolair; Novartis) every 4 weeks had been administered for 6 months. Eosinophils decreased from the start of omalizumab administration, but symptoms remained unimproved. Six months after changing to dupilumab (loading dose of 600 mg followed by 300 mg every other week, DUPIXENT; Sanofi), eosinophils were slightly increased, but subjective symptoms according to ACT and CAT along with FeNO and serum IgE were all improved. Serum eosinophil count decreased after omalizumab, but was slightly increased by dupilumab, without returning to the level seen before starting omalizumab (Table 1). FOT showed improved respiratory resistance (Figure 1).

Table 1. Comparison of characteristics before and 6 months after starting dupilumab in three patients with asthma-chronic obstructive pulmonary disease overlap

Characteristic	Case 1		Case 2		Case 3	
Dupilumab	Befor	After	Befor	After	Befor	After
Ege, Years	77		73		56	
Sex	male		female		male	
Smoking status (pack years)	35		Severe passive smoking		10	
Emphysema	++		+		+	
Previous biologics	mepolizumab		omalizumab		none	
$FEV_{1.0}$, L	0.87	0.82	1.35	1.58	2.48	3.03
$FEV_{1.0\%}$ ($FEV_{1.0}$/FVC)	29.2	28.5	56.5	64.2	60.3	68.4
FVC, L	2.98	2.88	2.39	2.46	4.11	4.43
V50/ L/s	0.19	0.25	0.68	1.15	1.4	2.37
V25/ L/s	0.14	0.10	0.08	0.14	0.27	0.67
ACT	11	16	15	23	17	22
CAT	20	16	17	5	24	16
FeNO, ppb	51	10	42	19	39	29
Serum IgE, IU/mL	1590	419	1422	71	1124	436
Eosinophil count,/ mL	57	374	288	410	1248	585
R5, cmH_20/L/S	5.24	4.90	3.30	2.95	2.49	2.30
R20, cmH_20/L/S	3.17	3.06	2.49	2.35	1.89	1.95
R5-R20, cmH_20/L/S	2.07	1.84	0.81	0.60	0.60	0.35

ACT, asthma control test; BA, bronchial asthma; CAT, chronic obstructive pulmonary disease assessment test; FeNO, fractional exhaled nitric oxide; $FEV_{1.0}$, forced expiratory volume in 1 second; IgE, immunoglobulin E; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5–R20, resistance at 5–20 Hz; VC, vital capacity; V50, maximum expiratory flow rate at 50% of vital capacity; V25, maximum expiratory flow rate at 25% of vital capacity.

Case 3 involved a 56-year-old man who had been admitted with bronchial asthma and eosinophil sinusitis. He had a history of smoking (Brinkman Index ≥200). Due to increased use of oral corticosteroid burst therapy, and the presence of eosinophilic sinusitis, home-based self-injectable dupilumab was started (loading dose of 600 mg then 300 mg every other week, DUPIXENT; Sanofi). After 6 months, lung function, subjective symptoms, FeNO, serum IgE, and serum eosinophil count were all improved (Table 1). FOT parameters also showed slight improvements (Figure 1).

In all three patients, subjective symptoms showed marked improvements, particularly sputum symptoms as unpleasant symptoms common to both asthma and COPD.

Whether "eosinophilic COPD", "COPD with coexistent asthma", and "smoking asthma" can be considered identical pathological entities remains contentious, but these three cases met the criteria for ACO.[1,12] Case 1 was classified as "eosinophilic COPD", while Cases 2 and 3 represented "COPD with coexistent asthma" or "smoking asthma". If an ACO patient remains uncontrolled despite maximal inhaler therapy, other treatment options may need to be considered.

Depressed sputum seemed to be an anti-IL-13 effect. IL-13 increases mucus production and inducible nitric oxide synthase in epithelial cells, mediating airway constriction. Moreover, IL-13 promotes goblet cell hyperplasia, leading to the transformation of bronchial fibroblasts into myofibroblasts.[15,16] Inhibitory effects on the secretion of sputum in these patients could be objectively evaluated not only by ACT and CAT but also by the FOT. In Cases 2 and 3, the effectiveness of dupilumab was attributed to effects on sputum-affected diseases such as peripheral airway lesion-predominant

COPD, so the anti-IL-13 component appears very effective.[15,16]

Similarities between COPD and asthma include inflammation and obstruction of the airway at the respiratory epithelial layer in both severe asthma and COPD, sharing a common feature of goblet cell metaplasia and squamous cell metaplasia.[17,18] However, the key cells and mediators in asthma and COPD differ. In asthma, eosinophils, mast cells, $CD4^+$ T-lymphocytes, and a smaller number of macrophages are the representative cells. Multiple inflammatory mediators are involved in asthma, such as histamine, leukotrienes, IL-4, IL-5, and IL-13. In COPD, neutrophils, $CD8^+$ T-lymphocytes, and macrophages with IL-8 and tumor necrosis factor α, among others, play a predominant role.[17] We expect future studies to clarify whether improvements in sputum symptoms are confined to eosinophilic pathologies.

In the present study, all three patients were effectively treated with dupilumab. Additional treatment with dupilumab appears promising, particularly when airway symptoms predominate and sputum is a frequent symptom of ACO.

Further studies are warranted to define ACO and validate the role of FOT in identifying ACO in clinical practice.

STATEMENT OF ETHICS

All three patients provided informed consent for the treatment and publication.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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