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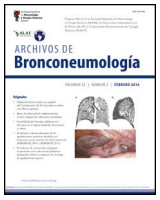

Clinical Letter

The Clinical Use of Dupilumab for Elderly Patients With Severe COPD Exacerbations: A Case Series

To the Director,

Chronic obstructive pulmonary disease (COPD) exacerbations are critical events that markedly accelerate the decline in lung function and worsen quality of life.[1] However, they remain inadequately addressed by conventional treatment (including bronchodilators, corticosteroids and antibiotics), particularly in severe cases. This underscores an urgent need for innovative strategies. Dupilumab, a fully human monoclonal antibody that dually blocks IL-4 and IL-13 signaling, offering a novel therapeutic option in multiple diseases characterized with type 2 (T2) inflammation.[2,3] Recent phase III trials demonstrated its potential in reducing moderate or severe exacerbations in patients with stable COPD exhibiting T2 inflammation features (blood eosinophils $\geq$300/μL).[4,5] Nevertheless, clinical data supporting dupilumab use during COPD exacerbation is lacking. Herein, we reported the first use of dupilumab in elderly patients with COPD exhibiting T2 phenotype and corticosteroid dependence during severe exacerbations.

We presented the first case of an 80-year-old male with a ten-year history of COPD who experienced recurrent dyspnea and wheezes triggered by *Pseudomonas aeruginosa* pneumonia, leading to hypercapnic respiratory failure (Table 1). Although pneumonia significantly improved after invasive mechanical ventilation, effective antibiotics, and systemic methylprednisolone, his symptoms persisted, accompanied with irreducible intravenous corticosteroids and elevated eosinophils (560/μL). The second case, a 79-year-old male presented with worsening dyspnea and disturbance of consciousness, requiring intubation and invasive mechanical ventilation. After receiving antibiotics against *Klebsiella pneumoniae* pneumonia, triple inhalation therapy and methylprednisolone, his condition improved but then deteriorated again during corticosteroid tapering. The hematology showed IgE 340 IU/mL and eosinophils rebounded from 80/μL to 760/μL. Our third case, a 71-year-old male was diagnosed with ever asthma and current COPD based on spirometry. He had been suffering from episodes of chest tightness and dyspnea, with cough and expectoration, after non-invasive ventilation and treatment against invasive pulmonary aspergillosis and pneumocystis pneumonia. He was identified as asthma-COPD overlap (ACO), relied on large doses of systemic corticosteroids and presented with elevated IgE level of 91 IU/mL and positive *Aspergillus fumigatus*-specific IgE. Although severe pneumonia improved, their hypoxic dyspnea persisted and failed to achieve a stable condition.

At diagnosis, the three elderly patients with severe COPD exacerbations were characterized with T2 phenotypes – one with elevated blood eosinophils, one with high serum IgE and rebounded eosinophils, and another with ACO and atopy (Table 1). There is a growing recognition that 20–40% of patients with COPD exhibit eosinophilic inflammation, indicating a T2 phenotype. This patient subset constantly experiences frequent exacerbations and responds favorably to corticosteroids.[6,7] At the onset of the exacerbations, defining their phenotypes was challenging due to the inhibitory effect of corticosteroid use on blood eosinophils. Expectedly, new biomarkers are emerging, such as atopy and fractional exhaled nitric oxide, beyond eosinophils.[8] Upon the corticosteroid withdrawal, all three patients were affiliated with episodic dyspnea, with eosinophil counts rebounded in cases 1 and 2, high levels of IgE found in cases 2 and 3. Due to their corticosteroid dependence and characteristics of T2 phenotypes, we firstly introduced dupilumab treatment after the peak of their severe exacerbations, to facilitate the rapid control of their symptoms and withdrawal of systemic corticosteroids, finally leading to successful outcomes. And no significant adverse effects were observed.

The mechanism of T2 inflammation in COPD has not been incompletely understood. While sharing certain similarities with asthma, anti-IL-5 (mepolizumab) or anti-IL-5 receptor (benralizumab) therapies targeting eosinophils have shown limited efficacy in COPD population, with no significant lung function improvement.[9,10] This therapeutic discrepancy highlights the involvement of other components in T2 inflammatory cascade. Preclinical studies implicated IL-4 and IL-13, key divers of T2 inflammation, contributed to airway remodeling and lung parenchyma destruction in COPD, and also promoted the activation and trafficking of eosinophils to airways.[11] By suppressing T2 inflammation in a broader way, anti-IL-4 receptor α antibody – dupilumab demonstrates superior clinical outcomes, including reduced exacerbations and improved lung function in COPD population with elevated blood eosinophils. As a fact, eosinophilic inflammation has been also observed in approximately 30% of exacerbations.[12] Although the role of dupilumab in the acute management of exacerbation has not been evaluated, its efficacy in the maintenance phase suggests potential benefits. The use of dupilumab at severe exacerbations could help corticosteroid tapering in these elderly patients, thereby avoiding adverse effects like hyperglycemia, secondary infections, osteoporosis, and adrenal insufficiency.[13]

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Table 1
Q3 The Baseline Characteristics, Disease Condition and Withdrawal of Systemic Corticosteroids in Three Cases With COPD Exacerbations Receiving Dupilumab.

Characteristics	Case 1	Case 2	Case 3
Age (year)	80	79	71
Gender	Male	Male	Male
Smoking status	Former smoker	Current smoker	Former smoker
*Smoking history (pack*year)*	100	100	20
COPD history (year)	10	–	3
Asthma history (year)	–	–	10
Background medication	Compound methoxamine intermittently	–	Budesonide/formoterol 320 μg/9 μg bid for 10 years, prednisone 10 mg bid in previous year
Cause of onset	*Pseudomonas aeruginosa* pneumonia	*Klebsiella pneumoniae* pneumonia	Invasive pulmonary aspergillosis, pneumocystis pneumonia
Severity of COPD exacerbation	Severe	Severe	Severe
PaO_2/FiO_2 ratio	162	112	144
$PaCO_2$ (mmHg)	>115	102	79
Respiratory support	Invasive mechanical ventilation	Invasive mechanical ventilation	Non-invasive ventilation
Antibiotics or antifungal agents	Meropenem, inhaled tobramycin	Ceftazidime/avibactam, colistin E nebulization	Isavuconazole, SMZ-TMP, caspofungin
Biomarkers of T2 inflammation			
Blood eosinophil, maximum (/μL)	560	760	10
Serum IgE, maximum (IU/mL)	95 (normal range <200)	340 (normal range <200)	91 (normal range <60)
Specific allergen	–	–	*Aspergillus fumigatus*
Initial dose of IvCS	MP 40 mg qd	MP 40 mg qd	MP 40 mg qd
Maximum dose of IvCS	MP 80 mg	MP 60 mg	MP 120 mg
Initiating time of dupilumab use	Day 5	Day 8	Day 26
Dupilumab use	Twice	Twice	Thrice
Withdrawal of corticosteroids			
Mean dose of IvCS before 1st injection	MP 53 mg qd	MP 40 mg qd	MP 68 mg qd
Reduction of IvCS after 1st injection[a]	42%	65%	18%
Reduction of IvCS after 2nd injection[a]	54%	80%	65%
Reduction of IvCS after 3rd injection[a]	–	–	93%
Persistent reduction of IvCS	After 2nd injection	After 1st injection	After 2nd injection
Total time from IvCS to OCS[d]	20d	9d	48d
Time from IvCS to OCS after 1st injection	14d	2d	23d
Time from IvCS to OCS after 2nd injection	3d	–	7d
Maintenance of OCS after last dupilumab use	17d	7d	9d
Clinical outcome	Improved, off the ventilator	Improved, with successful extubation	Improved
Sequential respiratory support	Nasal oxygen	Nasal oxygen, non-invasive ventilation alternatively	Nasal oxygen
Length of hospital stay (day)	28	25	66

Q4 COPD: chronic obstructive pulmonary disease; T2: type 2; SMZ-TMP: sulfamethoxazole-trimethoprim; IvCS: intravenous corticosteroids; OCS: oral corticosteroids (prednisone); MP: methylprednisolone.
[a] Reduction of IvCS was calculated on the percentage of mean doses of IvCS before 1st injection.

To our knowledge, our cases represented the first attempt to dupilumab use during COPD exacerbation, based on the comprehensive evaluation of T2 characteristics and clinical features. Dupilumab, as an add-on treatment, should be considered earlier, particularly in severe cases, rather than postpone to the stable phase, to manage symptoms better.

CRediT Authorship Contribution Statement

HC collected and analyzed the data, wrote and revised the manuscript. ZC helped the data analysis and prepared tables. HJ, QS, JB, LT and SJ shared responsibility for the diagnosis and treatment of three cases, and helped data interpretation. LW conducted the follow-up assessments of the cases. JJ reviewed the manuscript and provided critical discussions. JZ conducted the study, reviewed the manuscript and provided critical discussions. All authors have read and agreed to the final version of manuscript.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

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Conflict of Interests

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

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