

Interpretation of the key issues of expert consensus on immunomodulatory therapies for chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease. Its pathogenesis mainly involves airway remodeling and alveolar destruction caused by inflammatory response, protease anti-protease imbalance, oxidative stress, apoptosis and imbalance of compensation repair in lung structural cell.^[1] More recently, researchers have devoted considerable attention to the mechanisms related to immunology. Lung tissue structural cells and innate/adaptive immune cells jointly participate in and maintain the homeostasis of local tissue microenvironment. When the respiratory system is stimulated by different substances, the regional immune system shows different response characteristics, causing different physiological and pathological changes. Immunomodulatory treatment of COPD is one of the hot issues in clinical practices after the guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease (revised edition in 2021) was published.^[2]

On the basis of negotiation, the writing group for the expert consensus of immunomodulatory therapies for COPD proposed the following four recommendations for treating COPD with immunomodulatory therapies.

CERTAIN BIOLOGICAL AND CHEMICAL AGENTS HAVE IMMUNOMODULATORY EFFECTS ON COPD BY ENHANCING IMMUNE

FUNCTION AND IMMUNE CELL ACTIVITY: BACTERIAL LYSATES, PHOSPHODIESTERASE (PDE) INHIBITORS AND MACROLIDES

Bacterial lysates (Levels of evidence: Grade A)

Bacterial lysates have a protective effect, which induce a significant reduction of the symptoms related to respiratory infections,^[3] envisage a reduction in the number of acute exacerbations^[3,4] and a shorter duration of hospitalization, help to improve the patient's lung function and immune function^[5] Therefore, for patients with COPD who need antibiotics due to acute exacerbation of COPD or repeated bacterial infections in the past 1-year, bacterial lysate treatment can be considered.

PDE inhibitors (Levels of evidence: Grade B)

The principal action of PDE inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic adenosine monophosphate.^[6] PDEs are enzymes that impact a range of cellular functions by modulating levels of cyclic nucleotides. PDE3 regulates cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) concentrations in airway smooth muscle, such that inhibition results in airway smooth muscle relaxation. PDE4 regulates cAMP concentrations and is involved in

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Access this article online

Website:

www.intern-med.com

DOI:

10.2478/jtim-2022-0069

inflammatory cell activation. PDE inhibitors may reduce moderate and severe exacerbations, improve symptoms^[7] and lung function^[7] and the life quality of patients with COPD.^[8] However, a randomized, double-blind, placebo- and active-controlled, parallel-group study showed CHF6001, a novel inhaled PDE4 inhibitor had no effect in the primary lung function analysis, reduced moderate-to-severe exacerbations for specific patient subgroup with chronic bronchitis and eosinophil count ≥ 150 cells/ μL .^[9] The adverse reaction of PDE 4 inhibitor in digestive tract and so on limits its clinical application.^[2] For patients with chronic bronchitis, severe and extremely severe ventilation dysfunction under standard treatment with medicine of COPD (including inhalation of long-acting bronchodilators and inhaled corticosteroids treatment) but still have a history of repeated acute exacerbations, especially those with a history of hospitalization due to acute exacerbation, PDE inhibitor treatment may be considered. However, during the treatment period, the patient's body mass decline, digestive tract adverse reactions, *etc.* should be closely monitored. Patients with depressive symptoms should use this drug with caution. PDE inhibitor should not be used together with theophylline drugs.

Macrolides (Levels of evidence: Grade A)

It can effectively reduce the inflammation of patients with COPD by reducing the generation of inflammatory cells, inhibiting the inflammatory reaction mediated by inflammatory cells, promoting the early apoptosis of inflammatory cells, and reducing the secretion of mucus in the lower airway, so as to reduce the airway injury and the risks of exacerbations,^[10,11] improve the lung function and improve the quality of life of patients.^[12] At present, more evidence-based medical evidence is still needed for the best patients with COPD who benefit from macrolides and their adverse reactions.

VACCINATION AGAINST INFLUENZA AND PNEUMOCOCCAL INFECTION

Influenza vaccination (Levels of evidence: Grade A)

Influenza vaccination can reduce the total number of exacerbations,^[13] serious illness and death in COPD patients, especially in elderly patients with COPD.^[14] Therefore, influenza vaccination is recommended for patients with COPD.

Pneumococcal vaccinations (Levels of evidence: Grade A)

13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent Pneumococcal Polysaccharide Vaccine (PPSV23), are recommended for all patients ≥ 65 years of age. The PPSV23 is also recommended for younger COPD patients

with significant comorbid conditions including chronic heart or lung disease. The PCV13 has been shown to exhibit at least the same or greater immunogenicity than the PPSV23 up to two years.^[15] Overall, pneumococcal vaccination can reduce the possibility of acute exacerbation in patients with COPD and is beneficial.

STATINS AND VITAMIN D

Statins (Levels of evidence: Grade C)

In recent years, it has been found that statins may improve lung function and delay the deterioration of the disease in COPD.^[16] However, a population-based study showed that statin use may thus only associate with reduced risk of exacerbations in patients with COPD with coexisting cardiovascular disease, but not in patients with the most severe COPD without cardiovascular comorbidity.^[17] The therapeutic effect of statins on COPD needs to be further explored.

Vitamin D (Levels of evidence: Grade B)

Vitamin D has emerged to possess inhibiting effects on pulmonary inflammation while exaggerating innate immune defenses.^[18] Vitamin D supplementation to patients with severe vitamin D deficiency can effectively prevent the acute exacerbation of COPD, but more evidence-based medical evidence is still needed to verify.

IMMUNOTHERAPY WITH TRADITIONAL CHINESE MEDICINE

Certain Chinese medicine compound and Cordyceps preparations may improve the quality of life and reduce the probability of acute exacerbations in patients with stable COPD by regulating immune function and improving immune cell activity, for example, traditional Chinese medicine compound and Cordyceps preparation,^[19] acupoint application and combined needle.^[20]

Based on the Oxford Centre for Evidence Based Medicine level system (2001), there are several recommendations of immunomodulatory drugs for COPD (Table 1).

There are many kinds of immunomodulators with different effects. The clinical research evidence for the treatment of COPD needs to be further verified in the real world. For clinicians, the key to selecting appropriate immunomodulators lies in the correct understanding of their immunomodulatory mechanisms. The authors also hope to take the opportunity of the preparation of this expert consensus to further improve the understanding of the immune pathogenesis of COPD and find new targets for immunomodulation therapy. With the continuous increase of research evidence and the continuous

Table1: Grades of recommendations for immunomodulatory drugs of COPD

Immunomodulatory drugs for COPD	Strength of recommendation
Biological agents of microbial origin	
Bacterial lysates	A
BCG-polysaccharide nucleic acid	C
Immunomodulator of Klebsiella extract	C
Products of the human or animal immune system	
Thymosin	C
Chemosynthetic drugs	
Macrolides	A
Phosphodiesterase inhibitors	B
Pidotimod	C
Vitamin D*	B
Statins*	C
Other functional regulation preparations	
Influenza vaccines	A
Pneumococcal vaccines	A
New targeted anti-inflammatory drugs	
Anti-non-T2 inflammation biologics	C
Anti-type T2 inflammation biologics	C
Protease inhibitor	C

*indicates that there is less evidence of application in COPD and more evidence-based evidence is needed. COPD: chronic obstructive pulmonary disease.

accumulation of clinical experience, this expert consensus will be updated in due time.

Source of Funding

This work was supported by the Capital health development scientific research special project (first issue 2020-2z-40917) and the National Natural Science Foundation of China (grants No. 820900013, 820900014 and 82100031); International Practice Guide Registration Platform (Registration No. ipgrp-2022cn267).

Conflicts of Interest

None declared.

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How to cite this article: Sun L, Chen Y. Interpretation of the key issues of expert consensus on immunomodulatory therapies for chronic obstructive pulmonary disease. *J Transl Intern Med* 2022; 10: 277-280.