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Advances in Treatment of Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common and heterogeneous disorder. The current COPD treatment is restricted to bronchodilators like β_2 agonists and anticholinergic and anti-inflammatory drugs like corticosteroids. This requires a significant increase in the therapeutic options available for COPD that is closely related to the widening of knowledge on the underlying mechanisms of the disease. The great interest in the development of novel drugs that can interfere with the natural history of COPD leads to synthesis of numerous novel molecules.

COPD is a major global health problem. COPD is a preventable and treatable disease. This, in part, reflects a good understanding of the molecular mechanisms of COPD and the development of novel therapies that can improve the health outcomes of COPD patients.

Key Words: COPD – emerging therapy - anti-inflammatory - bronchodilator – cytokine – chemokine.

Introduction

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (cough, sputum production, dyspnea, exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and / or alveoli (emphysema) that cause persistent, often progressive airflow obstruction .[(1)] COPD is a major cause of morbidity and mortality worldwide. It is the third leading cause of death and the fifth cause of disability worldwide.[(2)] It is expected that the prevalence of COPD will increase over time; this requires new COPD therapeutic options to develop.[(1)]

The persistent exposure to inhaled irritants like cigarette smoke, indoor air pollution and occupational exposures, activates many pathways of inflammation which underlies the developpment of COPD by several ways leading to chronic bronchitis and emphysema.[(3)] Therefore, recent therapeutic strategies have targeted these inflamematory pathways.[(4)] Oxidative stress is another important mechanism underlying the pathogenesis of COPD that contributes to airway remodeling and emphysema. This leads to the development of new anti-oxidant drugs.[(5)]

COPD risk factors

COPD results from gene–environment interactions. The main risk factor is cigarette smoking. Other environment-

tal exposures such as indoor air pollution, especially from burning biomass fuel in confined spaces. Occupational exposures to chemicals and dusts, genetic abnormalities, including alpha1-antitrypsin deficiency due to mutations in SERPINA1 gene, and accelerated ageing can also contribute.[1]

COPD pathogenesis

COPD is the end result of complex gene–environment interactions over the lifetime that can damage the lungs. The observed inflammation in the respiratory tract of COPD patients appears to be a modification of the normal inflammatory response to the chronic irritants such as cigarette smoking. Excess proteinases in the lungs and oxidative stress are likely to further modify this inflammation.[1] COPD is characterized by increased number of macrophages in the lung parenchyma, peripheral airways and pulmonary vessels, together with increased activated macrophages and neutrophils. These inflammatory cells release multiple inflammatory mediators which attract inflammatory cells from the circulation and induce structural changes.[1]

Current therapies for stable COPD

I- Bronchodilators including beta$_2$-agonists. There are short-acting (SABA) and long-acting beta$_2$-agonists (LABA). Antimuscarinic drugs including short-acting (SAMA) and longacting muscarinic antagonists (LAMA).

II- Anti-inflammatory agents

including inhaled and oral glucocorticoids.

Emerging therapies

We will discuss the advanced drugs for COPD management in this review.

I-Smoking cessation

The only therapeutic intervention that has modified the accelerated rate of decline in FEV1 in COPD is smoking cessation. Some recent drugs have been developed to assist smokers in smoking cessation. Drugs like varenicline and bupropion are used as nicotine replacement therapies. Current studies focus on the development of antibodies against the circulating nicotine in the blood. There are three vaccines under development including CYT002-NicQb, Nicotine-Qbeta and NicVAX.[6]

II-Newer bronchodilators

Bronchodilators are the gold standard for COPD management. Short-acting bronchodilators (SABAs) have led to treatment noncompliance because of the need of several doses causing discomfort to the patient. This problem led to the development of both, long- acting and ultra-long acting bronchodilators that provide prolonged action lasting up to (12-24) hours.[7] In general, bronchodilators fall into two large categories: β_2- agonists and muscarinic antagonists.

***Ultra-long acting β_2 agonists (ultra-LABAs)**

The current ultra-LABAs under development include indacaterol, vilanterol, and olodaterol. Indacaterol has been approved in the USA and Europe as a bronchodilator. Vilanterol is an ultra-LABA that is found to be effective and safe in COPD patients in clinical trials.[7]

***Ultra-long acting muscarinic antagonists (ultra-LAMAs)**

The best bronchodilators used in COPD are ultra-LAMAs. LAMAs can reduce the exacerbation frequency. Some examples of the ultra-LAMAs being evaluated in clinical trials are aclidinium, darotropium, and RBx 343E48F0.[8]

***New combinations**

Some bi-functional bronchodilators are in different stages of clinical development. MABAs (muscarinic antagonist-β2 agonist) are currently under investigation.[9] MABAs are more likely to be

used in severe cases of COPD. MABAs, in combination with steroids, can reduce the frequency of COPD exacerbations. Some of these triple drug combinations that are under development: tiotropium + formoterol ± budesonide/fluticasone, glycopyronium + formoterol ± mometasone, and aclidinium + formoterol ± fluticasone/budesonide.[10]

III- New anti-inflammatory treatments

***PDE4 inhibitors**

Phosphodiesterase-4 (PDE-4), an isoenzyme of phosphodiesterase, is the predominant phosphodiesterase that is expressed in neutrophils, T lymphocytes and macrophages. Selective PDE4 inhibition may inhibit various inflammatory cells. Roflumilast, a selective oral PDE4 inhibitor, is approved for COPD as an anti-inflammatory drug. Inhaled PDE4 inhibitor in combination with a LAMA and LABA is being explored. The present PDE4 inhibitors have some intolerable gastrointestinal side effects; so specific PDE-4B and PDE-7 inhibitors are under development**.**[11]

***Antiproteases**

Proteases such as matrix metalloproteinase (MMP) are released from epithelial and inflammatory cells. MMP can destroy elastin causing pulmonary emphysema. MMP inhibitors can be used to prevent emphysema. Selective MMP inhibitors like inhibitors of MMP-9 and MMP-12 are in phase II and phase III clinical trials**.**[6]

***Cytokine Inhibitors**

Cytokines targeted for inhibition include interleukin (IL)-1β, and IL-6. IL inhibitors are being tested in COPD patients and still in the development phase.[6]

***Chemokine antagonists**

Chemokines such as CXCL1, CXCL5 and CXCL8 have chemotactic effects upon monocytes and neutrophils. These chemokines are mediated by a common receptor. Antagonists for these chemokine receptors are under development.[12]

***Nuclear factor-kB inhibitors**

Nuclear factor-kB (NF-kB) is a transcription factor that regulates the expression of MMP-9, chemokines, and TNF-α that play a key role in COPD inflammation. NF-kB inhibitors are still under development.[12]

***Antioxidants**

Oxidative stress contributes to COPD pathophysiology in multiple ways. The most widely used anti-oxidant is N-Acetyl-Cysteine (NAC). Erdosteine, carbocysteine, N-isobutyrylcysteine (NIC), and N-acestelyn (NAL), are other anti-oxidants under development. NAL is being tested in the clinical trials and found to be well tolerated. Inhaled preparations of anti-oxidants are under development**.**[5]

***Statins**

Statins have anti-inflammatory and antioxidant properties. Some studies have shown that statins might improve mortality, exacerbations, and exercise tolerance in COPD patients. Lipophilic statins including atorvastatin and simvastatin are likely to be more effective than pravastatin hydrophilic statin. These statins need further evaluation before their use in COPD management**.**[13]

IV-Lung regenerative therapies

Presently COPD is a progressive disease and managed only symptomatically. Any therapy that can restore the damaged lung tissue may be able to reverse the disease.

***Stem cells** Allogenic stem cells infusion may be a hope, as they can regenerate the destroyed alveolar tissue directly or by growth hormones secretion.

Trials investigating stem cells efficacy and safety in COPD patients are underway.

***Anti-ageing therapy**

Oxidative stress causing accumulating DNA damage is the hallmark of accelerated ageing implicated in COPD pathogenesis. It is mediated by silent information regulator two sirtuin1 (SIRT1) inactivation. Resveratrol that can be found in nuts and seeds is currently being studied as COPD therapeutic agent as it activates SIRT1. New activator of SIRT1 such as SRT501 is under development.[(14)]

Recommended vaccinations for COPD patients

Recommended vaccinations for COPD include influenza vaccination annually. Also, pneumococcal vaccination (PPSV23); Patients who received a vaccineation before the age of 65 needs another re-vaccination after age 65, with at least 5 years between doses.[(1)]

COVID-19 and COPD

COPD patients who present with worsening respiratory symptoms that could be related to COVID-19 should be tested for SARS-CoV-2 infection. COPD patients should follow the basic measures of infection control. COPD medications should not be changed during this pandemic. Spirometer is done only when essential. COPD patients should have the COVID-19 vaccination according to the national recommendations.[(1)]

Conclusion

Treatment for COPD that can reduce disease progression is lacking due to the deficiency in our understanding of the disease. We have highlighted some updates in COPD therapeutic modalities in this review. We wish that this review article will inspire more investigations that can facilitate further COPD personalized therapy.

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