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Recent Advances of Drugs in COPD

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ABSTRACT:

Multiple etiologies are linked to the condition known as “chronic obstructive pulmonary disease (COPD)”. It is the leading global cause of morbidity and mortality. Chronic bronchitis, emphysema, and airway remodelling are the hallmarks of chronic obstructive pulmonary disease (COPD), a lung condition that causes structural changes in both small and large airways as a result of subepithelial fibrosis, increased smooth muscle mass of the airways, neovascularization, and glandular hypertrophy. In every country in the world, its prevalence is rising daily. Few effective medications are currently available, but none of them can stop the disease from progressing or address all of its defining symptoms.

This study summarises some of the most recent developments because existing treatments only address a subset of symptoms and do not work to reverse the disease's defining characteristics.

INTRODUCTION:

Emphysema and chronic bronchitis are the two primary conditions that define chronic obstructive pulmonary disease (COPD), a lower respiratory tract illness. A set of lung conditions cause individuals to have trouble breathing by obstructing airflow. It is impossible to repair lung damage caused by COPD.

More than 70% of adults in the National Health and Nutrition Examination Surveys (NHANES) with chronic airway obstruction on spirometry did not have a formal diagnosis of COPD, according to an examination of the NHANES data (2). The active inflammatory processes that are linked to COPD can lead to increasing blockage of the small airways, degeneration of the lung parenchyma, and deterioration of lung function. A deeper understanding of the aetiology of COPD will help find new targets for treatment once some of its mechanisms are understood [3].

PATHOPHYSIOLOGY:

Smoking is the major cause of COPD. But some people smoke for years and never get COPD while some people don’t smoke still get COPD. A person with a rare condition in which they lack alpha-1 antitrypsin can develop emphysema even without smoking.

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Other risk factors may include workplace exposure to certain gases or vapours, exposure to smoke and pollution, or frequent use of open flames when cooking.

None of the continuing treatments can stop the disease's progression at this time. Inflammatory mechanisms that are active in COPD are linked to progressive small airway blockage, lung parenchyma damage, and a reduction in lung function. COPD is still being under- and incorrectly diagnosed. Shortness of breath, coughing, or mucus production that is acutely worse than normal day-to-day variation are signs of a COPD exacerbation. They are harmful events that accelerate the loss of lung function, increase mortality, deteriorate health status, and increase cardiac events along the course of the disease (1).

STRATEGIZING NEWER APPROACHES:

The hunt for new treatments has many facets, including 1) enhancing existing drug classes, 2) creating innovative treatments by a deeper comprehension of the disease processes, and 3) (4)

New inhaled glucocorticoids

"Inhaled corticosteroids (ICS) are new inhaled glucocorticoids that have been developed to": (1) have a strong anti-inflammatory effect when applied topically; (2) have long-lasting anti-inflammatory effects in the lower airways without significantly accumulating in the lung tissues; (3) have low systemic exposure; (4) have high clearance and the formation of inactive metabolites; and (5) be compatible with inhalers [5]. There aren't many novel inhaled glucocorticoids being developed at the moment.

Valsecorat (AZD7594), it is a non-steroidal, selective glucocorticoid receptor modulator that is breathed. The clinical trial is currently in phase 2 and was last updated in November 2021. It is currently in the early stages of clinical development (clinicaltrials. gov). It is a once-daily given chemical that has low solubility, which prolongs lung retention and may have a long-lasting anti-inflammatory impact on the airways. Systemic circulation absorption is very slow (6).

Newer inhaled (topical) β2-receptor agonists

Currently, stable COPD patients can tolerate long-term usage of long-acting/ultra-long acting inhaled 2-adrenoceptor agonists (LABAs/ULABAs) with little side effects. However, there is still interest in developing new pharmaceuticals that have fundamental structures that are distinct from those of the class's already existing medications (7).

Abediterol is a more recent and focused long-acting 2-agonist that can treat COPD with a once-daily dose. In comparison to current LABAs (formoterol and indacaterol), this medication in vitro and in vivo demonstrates superior bronchodilatory effects and similar to or greater selectivity for 2-receptors over 1- receptors [8]. Significantly, abediterol lasts about as long as or longer than other LABA molecules, but its impact on heart rate is weaker. The most recent clinical study update was in January 2019 and it is in phase 1 (clinicaltrials.gov)

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To assess abediterol, there has been a randomized, double-blind, cross-over, placebo-controlled phase 2 clinical trial (NCT01425814) to evaluate the pharmacodynamics of a DPI single dose in COPD patients [n=70, 26 females, mean age 61 years, mean forced expiratory volume in 1 sec (FEV1) 58%, 29 former smokers, mean pack-years (p-y) 49, n=49 GOLD stage II, n=21 GOLD stage III] randomized to a dose of abediterol 0.625 µg, 2.5 µg, 5 µg, 10 µg, indacaterol 150 µg or placebo. As compared with the placebo, all dose of abediterol significantly increases FEV1 and as well the higher doses of abediterol (2.5 µg, 5 µg, 10 µg) also significantly improved FEV1 as compared with indacaterol (9).

Abediterol is still under phase 2 development. (4)

Dual PDE3/PDE4 inhibitors

An isoenzyme PDE3 is expressed in smooth muscles of airway (10). When PDE3 inhibited, it leads to relaxation of smooth muscles of airway, whereas the inhibition of PDE4 isoenzyme suppresses airway inflammation. (11,12)

Therefore, drugs that block PDE3 and PDE4 will improve the condition of the airways by reducing inflammation and relaxing smooth muscle (13).

The mechanisms behind this ostensible synergistic impact of simultaneous PDE3/4 inhibition are yet unclear. (4) Peak FEV1 response and symptom improvement were observed in stable moderate COPD patients (n=405, 160 females, mean age 63 years, average FEV1 56%, 183 former smokers, mean p-y 42, not receiving regular bronchodilator therapy) receiving ensifentrine inhaler twice daily at different dosages (0.75 mg, 1.5 mg, 3 mg, and 6 mg) in a 4 week randomised, double blind, placebo-controlled, parallel- (on week 4 of treatment). (14). The clinical trial is in its third phase.

Improved intravenous recombinant human α1-antitrypsin

COPD is linked to an alpha-1 antitrypsin deficiency.

AAT-Fc fusion protein INBRX-101 was developed to safely obtain the same level of alpha-1 antitrypsin as that found in healthy humans. It also has an excellent safety profile.

INBRX-101 is the subject of this open-label, two-part, dose-escalating Phase 1 investigation (rhAAT-Fc). A single ascending dose (SAD) of INBRX-101 will be administered in Part 1 and multiple ascending doses (MAD) of INBRX-101 will be administered in Part 2. The intended dose schedule is IV every three to four weeks. (clinictrials.gov).

A novel human-derived protein called Human 1-antitrypsin Modified Process (1-MP) is prepared using a special manufacturing process and has an additional ion exchange chromatography to inactivate viral contamination (15).

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AAT deficient patients (n=4, age >20 years) who received a dose of iv 60mg/kg of AAT-MP once a week for 8 weeks showed an excellent tolerance capacity in a multicenter, open-label, phase 1 and 2 clinical trial (Study GTI1401, NCT02870309, completed in 2017) (16).

The GTI1401-OLE research is an ongoing extended trial (NCT02870348), and January 20, 2023 is the projected completion date. With safety (as evaluated by adverse events, discontinuations owing to adverse events, and COPD exacerbations) as the main focus, it will evaluate the impact of intravenous administration (60 mg/kg weekly) of AAT-MP in the same population (4)

CONCLUSION:

All over the world the prevalence of COPD is increasing day by day. There are effective treatments available for the disease but there is no any cure till now. So there are trials going on to improve the existing classes of drugs and recent advances by targeting new pathways.

For Numerous new clinical trials have been conducted in an effort to improve the medication classes now used to treat COPD. A non-steroidal, inhaled, selective glucocorticoid receptor modulator under early clinical development is called Valsecorat (AZD7594). Abediterol is a more recent and selective long-acting 2-agonist that is still in phase β2 development and has the potential to treat COPD with a once-daily dose. Ensifentrine Inhaler is undergoing phase 3 clinical studies for dual PDE3 and PDE4. An enhanced form of human recombinant 1-antitrypsin, INBRX-101 completed the first phase of the study. Despite all of these efforts, additional knowledge regarding the pathways that lead to the development and advancement of COPD is still needed in order to stop the illness from progressing.

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