

Pharmaceutical Therapies for Chronic Obstructive Pulmonary Disease Complicated by Pulmonary Hypertension

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As a chronic lung condition, chronic obstructive pulmonary disease (COPD) is well-known. As our understanding of COPD's consequences has grown, pulmonary hypertension (PH) has drawn a growing amount of attention. Patients' quality of life is significantly impacted by the higher mortality and poor prognosis of COPD patients with PH, and there are still no effective medications available to treat the condition. The development of medication therapy for COPD complicated by PH was examined in order to fully comprehend the state of the disease's treatment at the moment. The findings suggest that for COPD patients with PH, the underlying disorders should be treated as well as possible. Statin and fasudil may also be advantageous, although the impact of targeted medications is still debatable. The effectiveness of various medications for COPD will eventually need to be further elucidated by larger randomized controlled studies.

Keywords: Chronic Obstructive Pulmonary Disease; Pulmonary Hypertension; Pharmacology; Treatment; Outcomes

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Introduction

THE widespread chronic lung condition known as chronic obstructive pulmonary disease (COPD) is characterized by ongoing respiratory symptoms and restricted airflow. Currently, COPD is a serious health burden (1, 2). A frequent form of pulmonary vascular illness known as pulmonary hypertension (PH) is characterized by a progressive rise in pulmonary vascular resistance (PVR) and a rise in right heart afterload as the disease worsens (3, 4). With the condition progress, exercise capacity steadily decreases, and right heart failure may ultimately cause death. As awareness of COPD has grown in recent years, its comorbidities, particularly PH, have drawn more at-

tention.

Accordingly, COPD complicated by PH occurs 30% to 70% of the time, and the severity of COPD is correlated with pulmonary artery pressure (5). High mortality and poor prognosis among COPD and PH patients have a negative impact on patients' quality of life. According to data from the Swiss PH Registry and the UK ASPIRE Registry, despite having lower PVR and mean pulmonary arterial pressure (mPAP) elevations than the majority of PH patients, COPD patients with PH had the worst prognosis (6, 7). There is currently no specific approach for treating COPD complicated with PH, despite the fact that substantial advancements have been made in the treatment of

pulmonary arterial hypertension (PAH) and the prognosis of PAH patients in recent years. Therefore, the key to long-term therapy of COPD complicated with PH is discovering effective medications or innovative treatment approaches. The development of pharmacological therapy in COPD patients with PH is covered in this paper.

Single Medication Therapy for COPD

Long-term home oxygen therapy, the use of bronchodilators, glucocorticoids, expectorants, etc., and, if necessary, anti-infective medications, intravenous glucocorticoids, and/or mechanical ventilation are all part of the basic treatment for COPD. Some of these patients with hypoxemia can somewhat halt the progression of COPD-related pulmonary hypertension, but few patients' pulmonary arterial pressures recover to normal ranges, and the aberrant pulmonary vascular structure cannot be improved (8). It will not be elaborated on because the study's main objective is not to improve the treatment of disorders that underlie COPD.

Statin Therapy

Clinically, statins are used to reduce cholesterol levels. According to recent studies, statins can minimize thrombotic reactions, improve endothelial function, reduce inflammation and oxidative stress, restrict the proliferation of vascular smooth muscle cells, and have a general protective effect on blood vessels (9-12). These outcomes imply that statins may be useful in the treatment of PH and other vascular illnesses, as well as in the management of COPD and PH.

Accordingly, statins can help individuals with COPD and PH. Atorvastatin was used to treat COPD that was complicated by PH (13-15) and the data revealed that mPAP in the atorvastatin group was considerably lower than it was prior to treatment after 6 months, while placebo did not undergo any notable changes. The use of statins in the management of PH brought on by COPD demonstrated that patients' pulmonary artery systolic blood pressure fell, and their 6-min walking distance (6MWD) rose after taking statins (16). Retrospectively matched cohort research revealed that statin-taking COPD patients had a 22% lower chance of getting PH than those who did not (17). Patients with COPD may experience less PH if they take statins. The protection is dose- and time-dependent.

Finally, statins may be both safe and helpful for COPD patients who also have PH. This must be further confirmed, though, by carrying out more RCTs with bigger samples and longer observation periods.

Fasudil Therapy

Fasudil is an isoquinoline sulfonamide derivative that reduces pulmonary artery growth factor and prevents the division of pulmonary artery smooth muscle cells while increasing endothelium-dependent vasodilation via controlling protein phosphorylation of vascular smooth muscle myosin light chain. Through the aforementioned method, the medication lowers vascular pressure, further enhancing the cardiopulmonary function of PH patients.

Studies demonstrated that the pulmonary artery systolic blood pressure, arterial blood oxygen partial pressure, brain

natriuretic peptide 10 days later, and 6MWD were significantly different in COPD patients with PH who received fasudil 30 mg/d treatment and conventional treatment (19, 20). Additionally, fasudil treatment significantly improved the patients' blood oxygen saturation, arterial partial pressure of oxygen, pulmonary artery systolic blood pressure, and 6MWD, according to a meta-analysis of 1 245 patients with COPD and PH (21). The findings of the above trials indicate that fasudil is advantageous for COPD patients with PH, but more large-sample and prospective studies are required to validate this.

Targeted Medication Therapy

The use of targeted medications in COPD patients with PH is debatable because the majority of researchers think that these medications influence the body's hypoxia while widening blood vessels. The 2015 edition of the European Society of Cardiology Guidelines for Pulmonary Arterial Hypertension noted that the use of the current targeted medications for the treatment of PH in patients with COPD and PH is not advised because they have not been sufficiently investigated in other forms of PH (22, 23). However, the focus of contemporary research continues to be on specific medications like soluble guanylate cyclase agonists, endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase 5 inhibitors.

Prostacyclin Analogs

Vascular endothelial cells produce the vasoactive chemical prostacyclin, which is then released into the blood. It relaxes vascular smooth muscle mostly through promoting the synthesis of cyclic adenosine monophosphate. Prostacyclin protects cells and has anti-proliferative properties in addition to its vasodilator impact. Synthetic prostacyclin analogs include epoprostenol, iloprost, treprostinil, and beraprost, all of which are used.

According to studies, prostacyclin analogs have no effect on oxygenation and are useless in people with COPD and PH. Iloprost was inhaled in various doses (10 g, 20 g) by COPD patients with severe PH, and this not only did not enhance their 6MWD but worsened the oxygenation (24). In a trial of COPD patients with severe PH (mPAP > 40 mmHg), the patients' 6MWD increased after 30 min of iloprost, but this value recovered to the baseline level 2 h later, whereas oxygenation, blood pressure, and lung function did not change significantly (25).

However, other researchers have presented an alternative viewpoint. According to Bajwa et al., after 16 weeks of inhaled treprostinil in COPD patients with PH, the patients' 6MWD increased, some pulmonary function indicators decreased, and there was no negative effect on oxygenation (26). Iloprost inhalation improved pulmonary hemodynamics in COPD patients with PH, even those with severe PH, according to the findings of another trial, and arterial oxygenation was unaffected (27).

The effectiveness of prostacyclin analogs in treating COPD complicated by PH is debatable, and no trials have so far supported their long-term usefulness. To produce further scientific findings, additional lengthy prospective controlled research with sizable samples is required.

Endothelin Receptor Antagonists

Endothelin is a strong vasoconstrictor, and when it binds to

endothelin receptors A and B on the pulmonary vascular wall, it causes pulmonary vasoconstriction and encourages the proliferation of smooth muscle cells. Endothelin-endothelin receptor signaling is blocked by endothelin receptor antagonists, which have vasodilating and antiproliferative actions. The US Food and Drug Administration has authorized the endothelin receptor antagonists bosentan and ambrisentan, which are being used in clinical settings to treat PH (28).

Endothelin receptor antagonists, according to some studies, ought to be avoided in COPD and PH patients. After taking bosentan for 12 weeks, the patients' 6MWD, pulmonary function, pulmonary arterial pressure, maximal oxygen uptake, or regional pulmonary perfusion pattern did not improve. Additionally, the patients' arterial partial pressure of oxygen decreased, the alveolar-arterial gradient increased, and their quality of life significantly worsened (29). In a randomized controlled study (ARIES-3) examining the effectiveness of ambrisentan in PH, ambrisentan was administered for 24 weeks to 24 patients with COPD and PH, and their 6MWD decreased by 5 m (30).

Accordingly, Bosentan, however, may have a considerable impact on COPD worsened by PH. A total of 32 patients with severe COPD and increased pulmonary arterial pressure (mPAP was 375 mmHg) were enrolled and randomly assigned to the bosentan group or the placebo group. The mPAP and PVR were much lower, while their 6MWD was significantly higher (31). A total of 86 elderly individuals with stable COPD and PH were included in a retrospective study, and after a period of 12 weeks, it was shown that bosentan could not only lower pulmonary arterial pressure and treat the body's hypoxic condition, but it could also enhance cardiopulmonary function and be extremely safe (32).

Stronger findings on the therapeutic impact of endothelin receptor antagonists on COPD complicated with PH are required from more and larger scale randomized controlled trials.

Soluble Guanylate Cyclase Inhibitors

With or without nitric oxide (NO), soluble guanylate cyclase agonists promote the synthesis of cyclic guanosine monophosphate (cGMP), which further relaxes blood vessels by relaxing smooth muscle, lowering pulmonary arterial pressure. The most popular of these medications in clinical settings is riociguat.

According to Ghofrani et al., riociguat decreased mPAP by 11.4% and 14.8%, respectively, after 4 hours of administration in 10 patients who got 1.0 mg orally and 8 patients who got 2.5 mg orally. PVR was decreased by 15.3% and 33.0%, respectively, and oxygenation-related side effects were not seen (33). Riociguat was employed by Ghofrani et al. in a hypoxic mouse model, and their findings revealed that riociguat could reduce lung inflammation and fibrosis, remodel pulmonary blood vessels, and partially reverse PAP (34). The effects of riociguat on COPD complicated with PH were studied by Pichl et al. using a mouse model of cigarette smoke-induced emphysema (35). Their findings revealed that riociguat could reverse the PH value in mice and partially reverse the established emphysema. The PVR of the mouse model was significantly reduced after 4-7 months of riociguat treatment.

As there are currently only a small number of prospective trials on the use of riociguat in COPD complicated by PH, con-

clusions can only be drawn from their analysis. Although riociguat may be helpful for COPD complicated by PH, further prospective studies with sizable sample sizes are required to more fully assess its efficacy and tolerability.

Phosphodiesterase-5 Inhibitors

By inhibiting phosphodiesterase-5, phosphodiesterase-5 inhibitors (PDE-5i) can prevent the breakdown of cGMP, causing cGMP to build up in cells and promoting NO-mediated vasodilation. The majority of these medications are currently used to treat pulmonary hypertension as a first line of treatment, and numerous trials have been conducted to treat COPD complicated by PH. Sildenafil, tadalafil, and vardenafil are examples.

Accordingly, PDE-5i has an impact on arterial oxygenation without offering therapeutic advantages to COPD patients with PH. According to Blanco et al., Sildenafil can enhance pulmonary hemodynamics in COPD patients with PH during exercise or at rest but with the risk of decreasing arterial oxygenation (36).

Some academics mentioned that sildenafil can have clinical effects without having an impact on oxygenation. According to Alp et al., the mPAP was reduced and the 6MWD increased following 12 weeks of sildenafil treatment (50 mg, twice a day) in 6 patients with severe COPD and mild PH (37). The impact of sildenafil on COPD worsened by severe PH was researched by Vitulo et al. and found that the PVR and BODE index of 28 individuals were reduced after 16 weeks of oral sildenafil therapy, but the cardiac index and carbon monoxide diffusing capacity increased (38). Oxygenation was unaffected. Following administration of 27 mg, PDE-5i improved 6MWD in PH patients with secondary pulmonary disease/hypoxia (primarily COPD), and it was not discovered that PDE-5i use made hypoxia worse. Barnes et al. conducted a systematic review of the role of PDE-5i in the treatment of pulmonary arterial hypertension (39).

In conclusion, there remains a debate concerning PDE-5i's effectiveness in treating COPD that is complicated by PH. The use of PDE-5i in patients with COPD and PH was not advised in either the 2018 Cologne meeting or the 2015 version of the European Society of Cardiology Guidelines for Pulmonary Arterial Hypertension; more clarification will come through prospective randomized studies.

Inhalable Nitric Oxide

The most significant vasodilator made and released by endothelial cells is nitric oxide (NO). Guanosine triphosphate can be changed into cGMP by combining with soluble guanylate cyclase. This activation of the downstream cGMP-dependent protein kinase subsequently enables smooth muscle cells to relax, allowing blood vessels to widen and ultimately lower pulmonary arterial pressure.

According to the findings of a randomized controlled trial by Vonbank et al., oxygen therapy mixed with NO significantly decreased mPAP and PVR and enhanced cardiac output in 40 COPD patients with mild PH after 3 months of treatment (40), and peripheral circulation, oxygenation, and lung function were unaffected, and exercise tolerance was considerably increased. In the study by Hajian et al., six patients with COPD and PH received pulsed NO inhalation for 20 min, and changes in pul-

monary vascular diameter were quantified using computed tomography-based functional respiratory imaging. The patient's pulmonary vascular capacity increased by 7.06% and 5.37% after inhaling NO, but the patient's blood pressure and blood oxygen saturation were unaffected, and the patient's dyspnea was reduced compared to before inhaling NO (41).

Although these findings suggest that short-term treatment with NO and oxygen may be helpful for patients with COPD and PH, the long-term continuous treatment effect and the impact on exercise tolerance and quality of life are not taken into consideration, and additional clinical trials are required to clarify the efficacy.

Conclusion

It is essential to treat the underlying causes of COPD in people with PH, and recent research findings indicate that giving statins and fasudil to these patients may be helpful. However, patients must be willing to take these medications. It is still debatable whether it can profit from tailored medications. Additional long-term large-sample randomized controlled trials are required in the future to learn more about whether these patients can benefit from prostacyclin analogs, endothelin receptor antagonists, soluble guanylate cyclase agonists, and phosphodiesterase-5 inhibition. Targeted medications, such as inhalable NO and inhalable NO, are very advantageous. Additionally, more investigation into the underlying causes of COPD and PH may help in the development of fresh therapeutic approaches. ■

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