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Cutting edge of COPD therapy: current pharmacological therapy and future direction

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common global health problem with increasing incidence and mortality. Therefore, attempting to increase the awareness of COPD and disseminate an effective system of management for COPD is important for human health. The management of stable COPD should be based on the disease severity, which is assessed by the severity of airflow limitation, symptoms and risk of exacerbations. The current mainstay of COPD therapy is bronchodilators. Recent advances in the development of both long-acting muscarinic receptor antagonists (LAMAs) and long-acting β_2-adrenergic receptor agonists (LABAs) enable us to not only improve lung function, symptoms and quality of life, but also decrease the frequency of exacerbations and curb the rate of progression of airflow limitation. Because there are clinical phenotypes of COPD which have increased airway inflammation, inhaled corticosteroids are likely considered for a supplemental medicine added to an optimal long-acting inhaled bronchodilator regimen for frequent exacerbators and patients with the overlap COPD-asthma phenotype. To establish novel COPD therapies that can considerably reduce the disease progression and mortality as well as the comorbidities associated with COPD, new therapeutic targets that are involved in the pathophysiology of COPD are being investigated.

Keywords: COPD, Bronchodilators, LAMA, LABA, Inhaled corticosteroids, ICS/LABA, Anti-inflammatory treatment

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health issue with constantly increasing incidence and mortality. It is estimated that about 7 % of all individuals have COPD. Especially, the prevalence is up to 10 % in adults aged older than 65 years [1–5]. The actual prevalence would seem to be higher than that reported because COPD is greatly under-diagnosed as well as under-recognized. COPD is expected to become the third leading cause of death worldwide by 2020 [6].

COPD is associated with a chronic inflammatory response in the peripheral airways and lung parenchyma to long-term exposure of noxious particles or gases. In the majority of COPD cases, noxious agents in cigarette smoke cause this chronic inflammation. Its pulmonary component is characterized by airflow limitation that is not thoroughly reversible and usually progressive. The airflow limitation is caused by increased resistance of the small conducting airways and increased compliance of the lung as a result of emphysematous lesions [7].

The main symptoms of COPD are dyspnea and chronic sputum production. Exertional dyspnea is the usual early symptom of COPD. Although various factors are involved in causing dyspnea, airway narrowing is a cardinal factor associated with dyspnea [8–10]. Airway narrowing in COPD is mainly caused by wall thickening and fibrosis in the small airways, as well as collapse of the small airways during exhalation due to the loss of radial traction caused by breakdown of the lung alveolar tissue [11, 12]. The increased sputum production is due to the increase in goblet cells and mucus gland hyperplasia [13].

Because COPD cases have an irreversible airflow limitation and their pathological condition is usually progressive throughout life, both pharmacological therapy and nonpharmacologic therapies should aim to control symptoms, improve quality of life, improve exercise tolerability, prevent exacerbations, disease progression and

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comorbidities as well as improve the prognosis. Especially, the recent report shows that dyspnea is the most relevant factor inducing disability, decreasing dyspnea is important to improve the ability of COPD patients [14]. To achieve these goals, both pharmacological therapy and non-pharmacologic interventions including smoking cessation, reduction of other risk factors, vaccinations, oxygen therapy, and pulmonary rehabilitation should be conducted with appropriate assessments of the disease severity at the beginning of a patient's treatment as well as continuous evaluation to determine whether the patient has achieved an adequate response to therapy. Recent observations have supported the hypothesis that, in COPD patients, the "spill-over" of inflammatory mediators from the lungs into the circulation may cause systemic inflammation, which may initiate and worsen ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes [15]. Therefore, appropriate control of the comorbidities is also important for COPD patients [16, 17].

In this review, we provide an overview of the current pharmacological therapies for the clinical management of COPD, together with recent advances in long-acting bronchodilators. We also discuss novel therapeutic targets for the future pharmacological therapy of COPD.

Review

Current pharmacological therapy for COPD

(1) Bronchodilators

Bronchodilators are the main pharmacological therapy for patients with COPD. Bronchodilators should be added according to the patient's symptoms, risk of frequent exacerbations and severity of the airflow limitation. Bronchodilators can induce long-term improvements in symptoms and exercise capacity, even if there is no or only minimal spirometric improvement, because inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with COPD, resulting in improved exercise endurance [18]. Moreover, the recent report suggests that the effects of bronchodilators should be evaluated from the changes of airway resistance in the resting tidal volume range rather than FEV_1, especially in connection with the improvement of dyspnea [19]. Therefore, the effect of therapies should be determined based on not only forced expiratory volume in one second (FEV_1) but also decreasing airway resistance and improvement of hyperinflation, symptoms, health-related quality of life (QOL), exercise endurance and physical activity of the patients.

Bronchodilators can be administered by inhalation, orally, percutaneously, subcutaneously, or intravenously. Inhalation is the recommended delivery method for COPD patients because this way maximizes the bronchodilator's effect on the airways while minimizing systemic side effects. Delivery methods for inhalation include a metered dose inhaler (MDI), soft mist inhaler (SMI), dry powder inhaler (DPI) or nebulizer. MDIs, SMIs, and DPIs enable COPD patients to receive inhalation therapy more simply, improving compliance and reducing the need for additional medication. The choice of a delivery method for inhalation should be determined after careful evaluation of the COPD patient's clinical condition (degree of airway obstruction, comorbidities) as well as their ability to maneuverer an inhalation device and to generate sufficient inspiratory flow. These patient factors should be adjusted with the advantages and limitations of each inhaler [20].

Bronchodilators include β_2 agonists, anticholinergics, and also methylxanthine, which is not typically used these days. Because each bronchodilator has a different mechanism of action, the addition of other bronchodilators can be considered when monotherapy is inadequate to improve the symptoms of COPD patients. β_2 agonists activate β_2-adrenergic receptors on airway smooth muscle [21]. Because β_2-adrenergic receptors are coupled to a stimulatory G protein of adenylyl cyclase, this activation increases the intracellular level of cAMP, resulting in decreased calcium concentrations within cells and the activation of protein kinase A. Those changes inactivate myosin light chain kinase and activate myosin light chain phosphatase. Moreover, β_2-agonists open large conductance calcium-activated potassium channels, which induces hyperpolarization of the airway smooth muscle cells. These changes lead to smooth muscle relaxation and bronchodilation. Anticholinergics (muscarinic receptor antagonists (MRAs)) block the activity of the muscarinic acetylcholine receptor M_3 on smooth muscle cells and submucosal glands [22]. This reduces smooth muscle contraction and mucus secretion, resulting in bronchodilation. A methylxanthine is a competitive, nonselective phosphodiesterase inhibitor that increases the intracellular cAMP level and activation of protein kinase A, resulting in smooth muscle relaxation and bronchodilation [23].

(a) Short-acting bronchodilators

Short-acting β_2 agonists and anticholinergics can be used for COPD patients with mild intermittent symptoms [24, 25]. The onset of action by short-acting beta agonists is relatively rapid compared to anticholinergics, whereas the maximal efficacy of short-acting anticholinergics for bronchodilation in COPD patients is better than that of β_2 agonists. Combination therapy may be better because the combined use of a short-acting beta agonist with a short-acting anticholinergic achieves a greater bronchodilator response than either one alone [26], though monotherapy with a short-acting bronchodilator is also effective and acceptable.

Table 1 Summary of long-acting bronchodilators including combinations

	Dosing	Reported superiority over other long-acting bronchodilators or ICSs	References
LAMAs			
Tiotropium	once-daily	vs. salmeterol: trough FEV_1, improving dyspnea, health-related QOL, preventing exacerbations	27–40
Glycopyrronium	once-daily		41, 42
Aclidinium	twice-daily		43, 44
LABAs			
Salmeterol	twice-daily		46–48
Formoterol	twice-daily		49
Indacaterol	once-daily	vs. salmeterol or formoterol: trough FEV1 and improving dyspnea	50–53
Olodaterol	once-daily	vs. formoterol: health-related QOL	54–56
LABA/LAMA			
Umeclidinium -Vilanterol	once-daily	vs. umeclidinium or vilanterol: trough FEV_1, improving dyspnea, health-related QOL	60–63
Indacaterol -Glycopyrronium	once-daily	vs. tiotropium: trough FEV_1, improving dyspnea, health-related QOL, preventing exacerbations; vs. glycopyrronium: trough FEV_1, health-related QOL, preventing exacerbations; vs. indacaterol: trough FEV_1, improving dyspnea	64–66
LABA/ICS			
Fluticasone -Salmeterol	twice-daily	vs. salmeterol or fluticasone: trough FEV_1, health-related QOL, preventing exacerbation	48, 76, 77
Budesonid -formoterol	twice-daily	vs. formoterol: trough FEV_1, improving dyspnea, health-related QOL, preventing exacerbations	78, 79
Fluticasone furoate -Vilanterol	once-daily	vs. fluticasone furoate: trough FEV_1	80

(b) Long-acting bronchodilators (Table 1)

(b)-1 Long-acting anticholinergics The long-acting anticholinergics (long-acting muscarinic agents (LAMAs)) include tiotropium, glycopyrronium, aclidinium and umeclidinium. These agents have higher selectivity for M3 receptors than for M2 receptors and dissociate more slowly from the M3 receptors, which can provide longer-lasting bronchodilation [27–29].

Tiotropium is a once-daily long-acting anticholinergic agent with M1 and M3 selectivity, and has been the most studied agent for COPD. Studies have shown that tiotropium improved lung function (an increase of both trough FEV_1 and forced vital capacity (FVC)) and exercise endurance as well as health-related QOL, and reduced dyspnea and the risk of COPD exacerbations [30–36]. Studies have also suggested that tiotropium may slow the rate of decline in FEV1 in patients with moderate COPD [37–39]. In terms of safety issues, there is conflicting evidence of adverse cardiovascular effects from tiotropium. Recent meta-analyses suggested that the tiotropium Soft Mist Inhaler (Respimat®) was associated with a significantly increased risk of mortality [40, 41]. This risk was apparent for cardiovascular death in patients with severe COPD, and at a higher daily dose [41]. However, data from a long-term, randomized trial showed that tiotropium was superior in reducing all causes of mortality by 11 % compared with placebo [42]. Another more recent randomized, double-blind, parallel-group trial revealed no safety issues with the device, supporting the safety of the Soft Mist Inhaler device [43].

Glycopyrronium is a once-daily long-acting anticholinergic agent that also selectively inhibits muscarinic receptors with M1 and M3 selectivity [27]. It also significantly improves lung function (through FEV_1) and dyspnea and reduces exacerbations of COPD [44, 45].

Aclidinium is a twice-daily long-acting anticholinergic that selectively inhibits M3 muscarinic receptors [28]. Since aclidinium is shorter acting than tiotropium, twice-daily dosing is needed for better efficacy. Several trials showed significant improvements in the trough and peak FEV_1 [46]. Aclidinium also improves dyspnea and delayed the time to first exacerbation compared to the placebo control [46, 47].

Umeclidinium is a once-daily LAMA that acts preferentially on muscarinic M3 receptors, similar to tiotropium. It significantly increases the trough FEV_1 and also reduces rescue SABA use [48]. Umeclidinium was been developed for use in a combination inhaler with long-acting LABA vilanterol.

(b)-2 Long-acting β_2-agonists The long-acting β_2-agonists (LABAs) include salmeterol, formoterol, indacaterol,

olodaterol and vilanterol. Until recently, a long-acting anticholinergic was preferred over a long-acting β_2-agonist because LAMAs, which act effectively for 24 h by once daily dosing, seemed to be superior to LABAs, which required twice-daily dosing for better effects. Now that daily LABAs are available, the initial selection of a long acting bronchodilator is based on co-morbidities and side effects.

Salmeterol and formoterol are twice-daily LABAs used in the maintenance for COPD. Formoterol has a faster onset of action than salmeterol, and has also been demonstrated to be more potent. Both salmeterol and formoterol significantly improved lung function as well as dyspnea, decreased exacerbation rates and improved health-related quality of life compared to placebo [49–52].

Indacaterol is a once-daily LABA with a rapid onset and 24-h duration of bronchodilation. Indacaterol's long duration of action may be related to its high affinity for the lipid raft domain of the cell membrane [53]. Randomized controlled trials showed that indacaterol significantly improved the trough FEV_1 [54–56]. Indacaterol improved dyspnea and decreased the rate of exacerbations in COPD patients. The trials also showed that once-daily indacaterol was significantly more effective than twice-daily salmeterol or formoterol in terms of improving the lung function and reducing dyspnea [54, 56].

Olodaterol is a once-daily LABA with a rapid onset and long duration of action and is approved for the treatment of COPD in Europe and US. It is delivered via a soft mist inhaler. Clinical trials showed that olodaterol improved lung function including peak and trough FEV_1 and quality of life [57–59]. Adverse events with olodaterol were comparable to those of placebo.

Vilanterol is also a once-daily LABA with a rapid onset and long duration of action. However, so far, it is not available as a monotherapy. Vilanterol has been developed for combination inhalers with umeclidinium or fluticasone furoate.

(b)-3 Comparison between LAMAs and LABAs Because both LABAs and LAMAs are once-daily agents with a long acting duration, the question of which type is better for COPD patients may arise in the clinical setting. A randomized controlled trial has done the compared a once-daily LABA, indacaterol and a once-daily LAMA, tiotropium. A trial in which moderate-to-severe COPD patients were enrolled and observed over 26 weeks, showed that indacaterol significantly improved the trough FEV_1 and at 12 weeks was superior to tiotropium, whereas indacaterol lost this superiority at 26 weeks, though the effects of indacaterol and tiotropium on the trough FEV_1 were maintained in terms of differing from placebo [55]. This trial also showed that indacaterol improved dyspnoea (transitional dyspnoea index (TDI)) and health-related QOL (St. George's Respiratory Questionnaire (SGRQ)) better than tiotropium. In terms of reducing exacerbations, indacaterol did not appear superior to tiotropium. The two treatments were well tolerated and had similar adverse event profiles. Another randomized controlled trial in which moderate-to-severe COPD patients were enrolled and observed for 12 weeks, revealed that indacaterol significantly improved dyspnoea and health-related QOL, and reduced the use of rescue SABA compared to tiotropium, though there was no significant difference in FEV_1 between indacaterol and tiotropium at 12 weeks [60]. There was a randomized controlled trial in which patients with severe COPD and a history of at least one moderate to severe exacerbation in the previous 12 months were enrolled. This trial showed that both indacaterol and tiotropium similarly improved the trough FEV_1 as well as providing protection from exacerbations [61]. These trials suggested that once-daily indacaterol was at least as effective as a once-daily tiotropium in improving the clinical outcomes of patients with COPD.

(b)-4 Combination therapies Another type of long acting bronchodilator is additionally prescribed for COPD patients whose symptoms are not well-controlled with a single long-acting bronchodilator. A meta-analysis of five trials that assessed a combination therapy with a LAMA (tiotropium) plus a LABA (salmeterol, formoterol, or indacaterol) showed that a combination therapy provided only a small increase in the peak FEV_1 and a slightly better quality of life compared to tiotropium alone [62]. No difference was noted in exacerbations, symptom scores, or serious adverse events.

Recently, a combination umeclidinium-vilanterol dry powder inhaler has been approved for once-daily use for COPD. Clinical trials showed that umeclidinium-vilanterol increased the trough FEV_1 significantly more than umeclidinium, tiotropium or vilanterol monotherapy [63–66]. The combination inhaler also provided greater improvements in health-related QOL, and dyspnea scores compared with its mono-components and placebo [63]. The effectiveness of umeclidinium-vilanterol for the reduction of COPD exacerbations seemed to be similar to that of umeclidinium monotherapy [65].

Another once-daily dry powder inhaler containing the combination of indacaterol-glycopyrronium has been recently approved for COPD patients. The indacaterol-glycopyrronium combination inhaler was found to be superior to monotherapy with glycopyrronium, indacaterol, or tiotropium in terms of trough FEV_1 [67–69]. Indacaterol-glycopyrronium also decreased the use of rescue medication and risk of exacerbation, and improved the health-related QOL compared to monotherapy with glycopyrronium or tiotropium [68].

(c) Methylxanthine

Methylxantine is another option which may be considered as an additional therapy to bronchodilators and inhaled corticosteroids. Slow-release oral theophylline is usually used for COPD patients. Its bronchodilation effect is modest compared to inhaled bronchodilators. For effective bronchodilation, the plasma levels of theophylline needed to be in the 10 to 20 μg/ml range. Because theophylline can be toxic, close monitoring of the drug levels is required. In recent years, it has been reported that low-dose theophylline (about 5 μg/ml at plasma level) has anti-inflammatory effects in patients with COPD [70–73]. This anti-inflammatory effect is likely due to increasing HDAC2 expression and activity in the alveolar macrophages of patients with COPD [74–77].

(2) Inhaled corticosteroids

COPD is an inflammatory disorder characterized by both airway and systemic inflammation. Because inhaled corticosteroid (ICS) therapy appears to reduce the inflammation, it has been hypothesized that ICS therapy may improve clinical outcomes of COPD. A number of clinical trials, including the largest randomized controlled trial, found that ICS monotherapy decreased exacerbations and modestly slowed the progression of dyspnoea, but had minimal or no impact on lung function and survival in COPD patients [51, 78]. Therefore, ICS therapy should be added to basic treatment with bronchodilators for appropriate clinical phenotypes of COPD, not recommended as monotherapy for patients with stable COPD. These clinical phenotypes which need additional treatment of ICS include frequent exacerbators and patients with the overlap COPD-asthma phenotype because lung inflammation is prominent in these phenotypes [79, 80].

Previous trials suggested that ICS could be considered as part of a combined therapy with bronchodilators for the inhibition of COPD exacerbations in severe/very severe patients. In one trial, salmeterol plus fluticasone significantly improved lung function, health-related QOL, and reduced the rate of exacerbations compared to placebo, salmeterol alone, or fluticasone alone [51]. In another clinical trial, 1323 COPD patients with stable, mostly severe COPD were enrolled and randomly assigned to receive salmeterol plus fluticasone or tiotropium alone for two years. There was no difference in the frequency of exacerbations, though salmeterol plus fluticasone reduced mortality and improved health-related QOL [81]. On the other hand, a subsequent analysis of this trial revealed that pneumonia was significantly more frequent in the salmeterol plus fluticasone group, despite the lower mortality [82]. It has also been shown that another twice-daily combination inhaler, budesonide/formoterol, increased the trough FEV_1 with a significantly greater improvement than formoterol alone. The budesonide/formoterol group had a significantly prolonged time to first exacerbation versus the formoterol group and significantly greater improvements in secondary outcomes including symptom and health-related QOL [83, 84]. In addition to twice-daily combination inhalers, a once daily dry powder inhaler, containing fluticasone furoate and vilanterol, has been approved for the treatment of COPD in US. A multicenter, 24-week trial in which stable moderate-to-severe COPD patients were enrolled and randomly assigned to fluticasone-vilanterol, fluticasone, vilanterol, or placebo, showed that fluticasone-vilanterol modestly reduced the rates of moderate and severe exacerbation more than vilanterol alone [85]. The rate of pneumonia was increased in the fluticasone-vilanterol combination groups [85].

Because LAMAs have also been shown to prevent exacerbations [36, 39, 81] and two types of long-acting bronchodilators, LABA and LAMA, including a combination medication, are now prescribed for severe COPD patients, whether inhaled corticosteroids provided significant additional benefits to severe COPD patients who are treated with both two types of long-acting bronchodilators remained unclear. To address this question, the latest 12-month randomized-controlled trial studied 2485 severe COPD patients who had a history of exacerbations of COPD [86]. The patients received triple therapy consisting of tiotropium, salmeterol and fluticasone propionate during a 6-week run-in period. The patients were then randomly assigned to continued triple therapy or withdrawal of fluticasone in three steps over a 12-week period and were observed until week 52. The results showed that the corticosteroid-withdrawal group did not show worse results in preventing exacerbations and improving dyspnea than the corticosteroid-continuation group, though there were minor changes in the FEV_1 and health status in the corticosteroid-withdrawal group at week 52. This report suggests the possibility that additional ICS may not be needed for reducing the risk of COPD exacerbations if the severe COPD patients are treated with LABA and LAMA, though it is also possible that the necessity of additional ICS may depend on a COPD phenotype which is more inflamed or not.

(3) PDE-4 inhibitors

Phosphodiesterase 4 (PDE-4) belongs to the cyclic nucleotide phosphodiesterase (PDE) family and has four gene families (A–D) [87]. As other PDEs, PDE-4 hydrolyzes cyclic adenosine monophosphate (cAMP). PDE-4 inhibitors block the hydrolysis of cAMP, resulting in increased levels of cAMP within the cells. It has been shown that inhibition of PDE-4 decreases inflammation and may promote airway smooth muscle relaxation.

Roflumilast is an oral, PDE-4 inhibitor that is approved for COPD patients in the United States. Randomized controlled trials and a meta-analysis were performed to investigate the effects of PDE-4 inhibitors. A randomized controlled trial in which 3091 patients with COPD enrolled showed that Roflumilast significantly improved the trough FEV1 and decreased the rate of moderate to severe exacerbations during the 52 week trial [88]. In another trial, 933 patients with moderate to severe COPD were enrolled in and randomly assigned to roflumilast plus salmeterol or salmeterol alone and 743 patients were randomly assigned to roflumilast plus tiotropium or tiotropium alone [89]. Roflumilast significantly improved the trough FEV_1, though such side effects of nausea, diarrhea, and weight loss were more frequent in the roflumilast groups. A meta-analysis of 23 randomized trials of roflumilast or cilomilast (another PDE-4 inhibitor) versus placebo found that treatment with a PDE-4 inhibitor modestly improved FEV_1 and reduced the risk of exacerbations but had little effect on the health-related QOL [90]. Those studies suggest that oral PDE-4 inhibitors may be considered as an additional maintenance therapy for patients with severe COPD for preventing exacerbations. It has not been determined whether it provides additional benefits when combined with other medications (LABA and LAMA, or LABA and inhaled corticosteroids).

Novel therapeutic targets for the future pharmacological therapy of COPD

An important goal of COPD management is to reduce disease progression, prevent exacerbations, and reduce the mortality rate. Although recent advances in bronchodilators have enabled significant bronchodilation effects and improvement of the symptoms and quality of life, current therapies including long-acting bronchodilators fail to substantially reduce disease progression, mortality and the risk of exacerbations because bronchodilators don't have significantly anti-inflammatory effects. It has been shown that COPD is associated with chronic inflammation in peripheral airways and lung parenchyma as well as systemic inflammation causing comorbidities including cardiovascular diseases. Therefore, it is natural that effective anti-inflammatory treatment would be necessary for reducing the disease progression and the mortality of COPD patients. However, no current therapies including inhaled

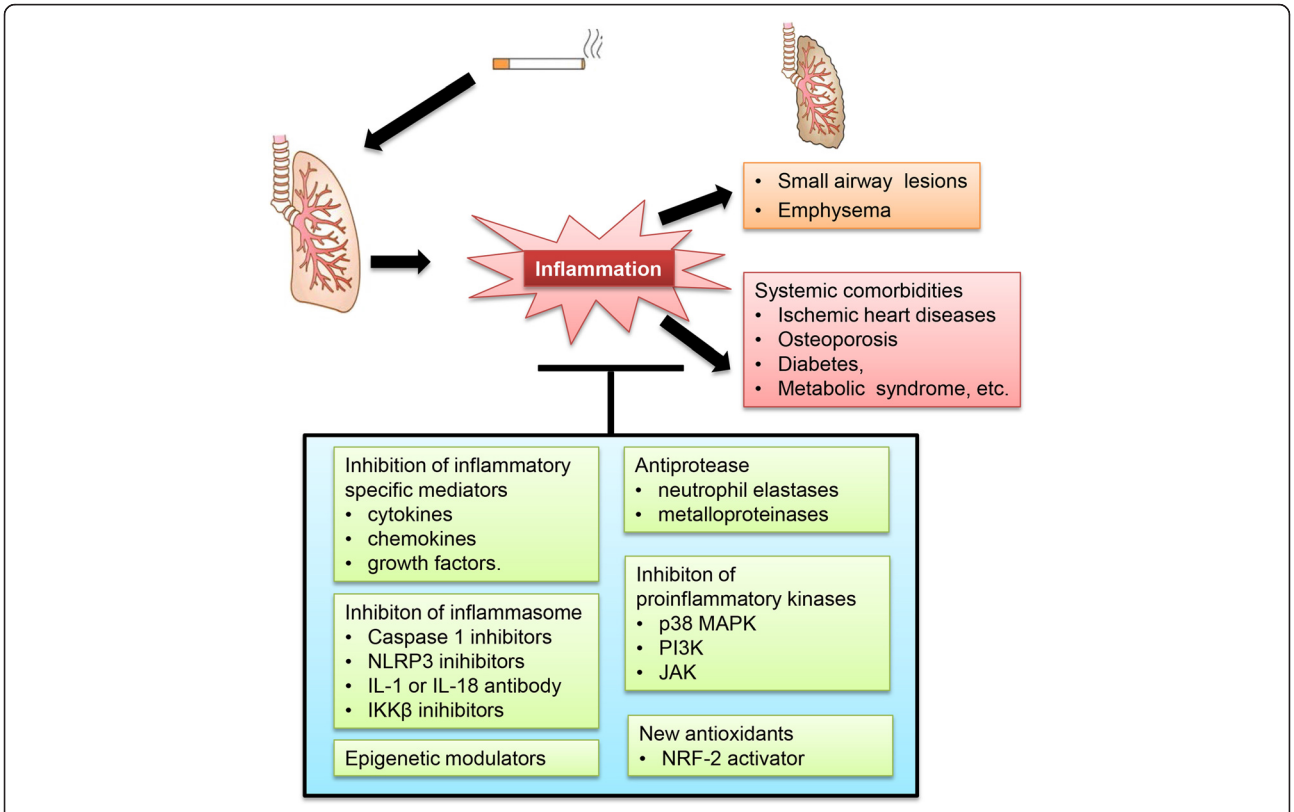

Fig. 1 Therapeutic targets for future pharmacological therapy of COPD. Recent advances in the research of underlying chronic inflammation provide new therapeutic targets for COPD patients. These possible therapeutic approaches include new antioxidants, inflammasome inhibitors, antagonists of cytokines or chemokines, inhibitors for pro-inflammatory kinase, antiproteases, and epigenetic modulation. IKK: inhibitor of NF-κB kinase; IL: interleukin; JAK: janus kinase; MAPK: mitogen-activated kinase; NRF-2: NF-E2-related factor; NLRP3: NOD-like receptor family, pyrin domain containing 3; PI3K: phosphoinositide 3-kinase

corticosteroids and PDE-4 inhibitor is sufficiently effective to treat the underlying inflammation in COPD patients.

Recent advances in the research of the underlying inflammation have been suggesting new therapeutic targets for anti-inflammatory treatments in COPD patients (Fig. 1) [91]. These possible therapeutic approaches include new antioxidants, inflammasome inhibitors, antagonists of cytokines or chemokines, inhibitors for pro-inflammatory kinase, antiproteases, reversal of steroid resistance, and epigenetic modulation, some of which are undergoing clinical trials.

It has been suggested that there are barriers to establishing new therapeutic approaches for COPD [91, 92]. These barriers include incomplete understanding of the underlying mechanisms of COPD, lack of an appropriate animal model, the heterogeneity of the disease, lack of biomarkers for predicting therapeutic response and long-duration trials needed for demonstration of clinical efficacy. Moreover, it is also important to accomplish complete pathophysiological evaluation and characterization of COPD patients to select an appropriate treatment for each clinical phenotype of COPD in order to achieve the best management. Therefore, further investigations for better understanding of the biological and pathophysiological processes of COPD are needed to achieve the goal of COPD management.

Conclusion

Recent advances in the development of long-acting bronchodilators have enabled significantly improvements in the symptoms and lung function of COPD patients. These reagents also reduce the risk of exacerbation and the rate of the progression of airflow limitation to some extent. To establish novel COPD therapies that can substantially reduce disease progression, mortality and the comorbidities, new therapeutic approaches that can resolve the underlying chronic inflammation and lung pathophysiological modifications in COPD are needed, and are being investigated.

Abbreviations

cAMP: cyclic adenosine monophosphate; COPD: Chronic obstructive pulmonary disease; DPI: Dry powder inhaler; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; ICS: Inhaled corticosteroid; LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonists; MDI: Metered-dose inhaler; QOL: Quality of life; SABA: short-acting β2-agonist; SGRQ: St. George's respiratory questionnaire; SMI: Soft mist inhaler; TDI: Transition dyspnea index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Both authors contributed to writing the manuscript. Both authors read and approved the final version of the manuscript.

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