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REVIEW

Positioning new pharmacotherapies for COPD

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Abstract: COPD imposes considerable worldwide burden in terms of morbidity and mortality. In recognition of this, there is now extensive focus on early diagnosis, secondary prevention, and optimizing medical management of the disease. While established guidelines recognize different grades of disease severity and offer a structured basis for disease management based on symptoms and risk, it is becoming increasingly evident that COPD is a condition characterized by many phenotypes and its control in a single patient may require clinicians to have access to a broader spectrum of pharmacotherapies. This review summarizes recent developments in COPD management and compares established pharmacotherapy with new and emerging pharmacotherapies including long-acting muscarinic antagonists, long-acting β-2 sympathomimetic agonists, and fixed-dose combinations of long-acting muscarinic antagonists and long-acting β-2 sympathomimetic agonists as well as inhaled cortiocosteroids, phosphodiesterase inhibitors, and targeted anti-inflammatory drugs. We also review the available oral medications and new agents with novel mechanisms of action in early stages of development. With several new pharmacological agents intended for the management of COPD, it is our goal to familiarize potential prescribers with evidence relating to the efficacy and safety of new medications and to suggest circumstances in which these therapies could be most useful.

Keywords: COPD phenotypes, once-daily inhalers, fixed-combination inhalers, long-acting muscarinic antagonist, LAMA, long-acting β-2 sympathomimetic agonist, LABA

Introduction

COPD is characterized by chronic airway inflammation related to the inhalation of noxious particles or gases.[1] The degree of inhalational injury varies and is influenced by genetic differences in individual susceptibility.[2] Both factors account for remarkable heterogeneity in the clinical manifestation of COPD. Tobacco smoking accounts for at least 80% of the burden of COPD, while other contributors include occupational and environmental exposures to dust or fumes.[3] COPD affects approximately 8% of the world's population, equating to approximately 160 million people,[4,5] and it has been the third-leading cause of death worldwide.[6] The clinical course typically evolves over several decades and early symptoms are often subtle. Disease progression in COPD is characterized by worsening airflow limitation, exacerbations occurring in varying frequency, impairment of exercise performance, and decline in health status. Management of COPD imposes a substantial economic burden, much of which is attributed to the treatment of acute exacerbations.[7]

Treatment of COPD can be classified as preventative, pharmacological, nonpharmacological, and surgical. The most important aspect of preventative management is avoidance of any potentially toxic exposures, especially smoking cessation, since this alone has been shown to alter the progression of the disease, at least in terms of the rate of decline in lung function.[8] If we consider decline in functional capacity as an important aspect of disease progression, then it is important to acknowledge that exercise

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programs can prevent the decline of physical activity.[9] Other preventative strategies include influenza and pneumococcal vaccination.[1] Traditional approaches to the pharmacological treatment of COPD include short- and long-acting inhaled bronchodilator therapies, inhaled corticosteroids (ICSs), and methylxanthines. The basis of nonpharmacological treatment is recognizing the need for supplemental oxygen and pulmonary rehabilitation.[1] Surgical options for severe COPD include lung volume reduction surgery, endoscopic lung volume reduction, and lung transplantation. In patients with upper lobe-predominant emphysema and poor exercise capacity, lung volume reduction surgery has shown a survival benefit.[10] Endoscopic lung volume reduction is a less invasive experimental approach that is continuing to be investigated. Arguably, lung transplantation is becoming a less attractive treatment recommendation for COPD, as the survival benefit has been questioned[11] and newer approaches to medical management continue to improve patient-reported outcomes.

The long-acting inhaled bronchodilators fall into two classes: long-acting muscarinic antagonists (LAMAs) and long-acting β-2 sympathomimetic agonists (LABAs). Over the past 10 years, the once-daily LAMA, tiotropium, and the twice-daily LABAs, salmeterol and formoterol, became widely prescribed for COPD. Several ICSs have also been available, some in a fixed-dose combination with a LABA. At the time of this review, several new inhaled and oral therapies have been introduced for the management of COPD and the data for their use are still limited (Table 1). Current guidelines have yet to incorporate these new therapies, suggesting the need for new treatment algorithms, such as those based on clinical staging and clinical phenotyping.[12,13] This article summarizes evidence for the efficacy and safety of new therapies and suggests how they might be utilized in such algorithms.

Established pharmacotherapy

Several guidelines exist for the management of COPD, including strategies for the selection of inhaled and other pharmacotherapies.[1,14–16] These guidelines are constantly evolving. Inhaled bronchodilator therapy is generally accepted as a first-line therapy for symptomatic COPD because evidence has shown improvement in dyspnea, exercise performance, reducing exacerbations, and overall health status.[1] This approach differs from asthma, where ICSs are regarded as the first-line therapy for persistent symptoms because of their ability to suppress airway inflammation.[17,18] Although there are many similarities in symptoms between

Table 1 New pharmacotherapies in COPD management

	Agency approval	Indication	Efficacy				Safety and adverse effects	General remarks
		GOLD grade	FEV_1 improvement	Exercise	Exacerbations	Health status and symptoms		
New LAMA monotherapy								
Aclidinium	US, EU	GOLD B, C, D	‡	‡	‡	‡	Bronchospasm, nasopharingitis (6%), headache (5%), dry mouth (<2%)	Faster onset of action to tiotropium, better nighttime FEV_1, BID dosing
Glycopyrronium	EU	GOLD B, C, D	‡‡	‡	‡	‡	Antimuscarinic and cardiac side effects similar to placebo	Rapid onset, very good safety profile
Umeclidinium	US, EU	GOLD B, C, D	‡	‡,•	‡,•	‡,•	Minimal antimuscarinic side effects	Combined with vilanterol
New LABA monotherapy								
Indacaterol	US, EU	GOLD B, C, D	‡‡	‡	‡	‡	Cough (6.5%), headache (5.1%), nausea (2.4%)	Improved cardiovascular safety profile and lung function compared to salmeterol
Vilanterol	US, EU	GOLD B, C, D	‡	‡,•	‡,•	‡	Nasopharingitis (10%), headache (9%), dry mouth (<10%)	
Olodaterol	US	GOLD B, C, D	‡	‡	–	‡	Nasopharyngitis (11%), dizziness (>2%), rash (>2%), arthralgia (>2%)	
Abediterol	–		‡‡					Better lung function impact in comparison to indacaterol

New LAMA-LABA combination therapy							
Umeclidinium and vilanterol	US, EU	GOLD C, D	+++	++	++	No increase in adverse events compared to placebo	First LAMA-LABA approved by the US FDA for maintenance treatment
Glycopyrronium and indacaterol	EU	GOLD C, D	+++	+++	+++	No increase in adverse events compared to tiotropium or glycopyrronium alone	Significantly better FEV_1 and SGRQ compared to tiotropium and glycopyrronium alone
Tiotropium and olodaterol	–	GOLD C, D	+++	+	+++	No significant difference in adverse events compared to monocomponents	Significant improvement in SGRQ score was only seen in the 5/5 μg dosing
Aclidinium and formoterol	EU	GOLD C, D	+++	–	–/++	Nasopharingitis (7.8%), headache (7.5%)	Significant improvement in FEV_1 1-hour postdosing compared to monocomponents
Glycopyrrolate and formoterol		GOLD C, D	+++				Improvement in FEV_1 from 0 hours to12 hours versus monotherapy with glycopyrrolate, formoterol, or tiotropium
New LABA-ICS combination therapies							
Vilanterol and fluticasone	US, EU	GOLD C, D	+	+++		Compared to vilanterol alone, FDC leads to an increased risk of pneumonia	Once-daily FDC of LABA-ICS
Indacaterol and mometasone	–	GOLD C, D	++				
Formoterol and ciclesonide	–	GOLD C, D	++		++	Oral candidiasis was the most common adverse event	Noninferiority comparison to combined fluticasone propionate/salmeterol in asthma
Formoterol and fluticasone	EU, Japan	GOLD C, D	+++			Approved for asthma, but in Phase III clinical trials for moderate to severe COPD	More rapid bronchodilator effect than fluticasone propionate/salmeterol
Triple LABA-LAMA-ICS therapy	–	GOLD C, D	++	–	++	No significant difference in adverse events compared to dual or monocomponents	A 40% reduction in mortality compared with ICS/LABA in a retrospective analysis
Dual muscarinic antagonist–β2-agonists	–		++[a]			Transient hypokalemic effect in 3/41 patients receiving additional high-dose salbutamol	GSK961081 has demonstrated effective bronchoprotection in early trials
Oral medications							
Roflumilast	US, EU	GOLD C, D	++[a]	++	–	Weight loss, nausea, diarrhea, and psychiatric symptoms	Recommended use only in advanced COPD as an add-on therapy
Azithromycin	US, EU	GOLD C, D		++		QT interval prolongation, ototoxicity, and drug–drug interactions	Careful risk–benefit assessment given the side-effect profile
Moxifloxacin	US, EU	GOLD C, D		++	–/++	Significant GI side effects compared to the placebo group	Intermittent pulsed therapy with 5 days of moxifloxacin every 8 weeks for six courses
Simvastatin	US, EU	GOLD C, D		–	–	No significant difference in fatal or nonfatal adverse events	No significant difference in exacerbations in one randomized, placebo-controlled trial

Notes: –No improvement in the published literature; +nonsignificant improvement; ++significantly improved compared to placebo; +++significantly improved to other drugs of the same class; *in combination therapy; [a]improved FEV_1 from baseline.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; LAMA, long-acting muscarinic antagonist; US, United States; EU, European Union; BID, twice daily; LABA, long-acting β-2 sympathomimetic agonist; FDA, Food and Drug Administration; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; ICS, inhaled corticosteroid; FDC, fixed-dose combination; GI, gastrointestinal.

COPD and asthma, the pathophysiologic differences between toxic and allergic airway inflammation account for differences in approaches to treatment and treatment responses. Despite these differences, the management of COPD may benefit from an algorithm similar to asthma that identifies people suffering from COPD with persistent symptoms. Such patients would be candidates for the introduction of daily maintenance therapy in the form of long-acting bronchodilator therapy.

A reduction of exacerbations is also an important goal in COPD management because of their significant impact on health status, exercise performance, health care expenditure, and survival.[19] Exacerbations are uncomfortable and distressing to people with COPD, and they reduce their health quality. At the same time, the impact on exercise performance reduces the possibility of an active life. Long-acting bronchodilators are effective at reducing exacerbations and include LAMAs and LABAs as the mainstay of therapy. Long-acting bronchodilators also improve exercise performance[20] and enhance the benefits obtained from a structured exercise rehabilitation program.[21] At this stage, no treatment, apart from supplemental oxygen, has convincingly shown a reduction in COPD mortality. In a 4-year randomized clinical trial, the LAMA tiotropium showed a reduction in mortality compared to placebo at 4 years,[22] and in a 3-year randomized clinical trial, the combination of LABA-ICS compared with placebo also showed a reduction in mortality, but both failed to achieve statistical significance.[23] As further data accumulate, it is postulated that bronchodilator therapy will prove to alter disease progression in COPD by reducing exacerbations portending a mortality benefit.

ICSs also reduce exacerbations in patients with severe COPD (forced expiratory volume in 1 second [FEV_1] <50% of predicted).[24–26] Furthermore, when combined with a LABA in patients with severe COPD, ICS produces additional benefits including improvements in pulmonary function and reductions in exacerbation frequency.[23,27] In patients with severe COPD, it is hypothesized that a reduction in airway inflammation and bronchial wall edema account for pulmonary function improvement. However, paradoxically, there has been a higher reported incidence of pneumonia in patients receiving ICS.[28,29] The reduction in exacerbations, and yet the increased risk of pneumonia, appears to be contradictory at face value. One explanation is that, despite the reduced airway inflammation and improved lung function, the effects of ICSs on local immune response mechanisms may allow for invasive bacterial infection.

New LAMA monotherapy

Aclidinium

Long-acting anticholinergic agents are considered the most effective class of bronchodilators for COPD.[1,14] While tiotropium was launched in 2004 and was the only available long-acting anticholinergic bronchodilator marketed for COPD until recently, there are now other LAMAs in various stages of trial development or regulatory approval.[30–33] Aclidinium bromide (Tudorza) is a LAMA that was simultaneously approved in the United States and Europe in 2012 for the maintenance treatment of COPD. The drug is formulated as a dry powder and delivered via a novel multidose inhaler (Pressair in the US; Genuair® in the European Union [EU]) at a US Food and Drug Administration (FDA)-approved dose of 400 μg twice daily. Twice-daily aclidinium significantly improved pulmonary function (FEV_1), dyspnea, and health status, and it was well tolerated in patients with COPD.[34,35] In one study assessing 24-hour pulmonary function in people suffering from COPD, aclidinium 400 μg twice daily provided clinically meaningful improvements compared to placebo with an effect size compared to tiotropium 18 μg once daily.[36] Compared to placebo, significant changes from baseline FEV_1 were detected 15 minutes postdose of aclidinium, with a peak effect at 2 hours at a time when aclidinium was no longer detectable in plasma.[37] This interesting feature of aclidinium probably reflects rapid plasma hydrolysis, which might account for reduced systemic exposure and a lower reported incidence of anticholinergic side effects. In registration studies, the incidence of anticholinergic adverse events was low, and similar to placebo.[34–36,38–41] Furthermore, aclidinium is reported with minimal cardiovascular risks.[34,36,42] Another potential advantage over tiotropium is that aclidinium reaches therapeutic levels within 2 days, which is compared to more than 7 days for tiotropium. An obvious disadvantage is the need for twice-daily dosing, but as a result of this, aclidinium is reported to give higher nighttime FEV_1 values and lower overnight COPD symptom scores.[36]

Glycopyrronium

Glycopyrronium bromide is a synthetic quaternary ammonium compound with a nonselective affinity for all five muscarinic receptor subtypes. Its prior use as a systemic anticholinergic medication has included control of oral secretions, control of urinary incontinence, and vagal blockade during cardiac surgery. Although the systemic formulation was never approved for the treatment of COPD, an inhaled formulation has now been developed for once-daily COPD treatment.[43,44] Its relative kinetic selectivity for the M3 versus

M2 receptors facilitates airway smooth muscle relaxation. In terms of its bronchodilator effects, glycopyrronium has demonstrated superiority compared to placebo.[45,46] In comparison with tiotropium, it showed a faster onset of action[47] and a significantly higher FEV_1.[45] Glycopyrronium significantly reduced the risk of COPD exacerbations by 31% compared with placebo. Treatment with glycopyrronium bromide also improved exercise endurance time and inspiratory capacity in patients with moderate to severe COPD, suggesting a beneficial effect on dynamic hyperinflation, which is compared to other LAMAs such as tiotropium and aclidinium.[47] Glycopyrronium has a higher incidence of dry mouth, but a favorable safety profile with an overall incidence of adverse events similar to placebo.[47] Glycopyrronium (Seebri®) was approved in the EU in 2012 and is delivered via a novel dry-powder inhaler (Breezhaler®).

Umeclidinium

Umeclidinium bromide is a LAMA that has been developed and approved for both monotherapy and combination use in the maintenance management of COPD. Clinically significant and important improvements in lung function were observed over a 24-hour period, indicating that umeclidinium would be an effective COPD medication and suitable for once-daily dosing.[48] In a randomized, placebo-controlled trial, umeclidinium at doses of 62.5 µg and 125 µg over 12 weeks improved pulmonary function (weighted mean FEV_1), breathlessness, and health status.[49] Umeclidinium was well tolerated over a wide range of doses in patients with COPD with no clinically significant adverse effects.[49,50] Umeclidinium (Incruse™) was approved by the US FDA in April 2014 as a monotherapy with a dose of 62.5 µg once daily. It is formulated as a dry powder and is delivered via a novel inhaler (Ellipta®).

New LABA monotherapy

Indacaterol

Indacaterol is a LABA with stronger affinity toward β-2 adrenergic receptors when compared to salmeterol. In addition to once-daily dosing, other advantages include longer duration, faster onset of action, and an improved cardiovascular safety profile when compared to salmeterol.[51] Indacaterol was shown to be superior in bronchodilator efficacy and clinical outcomes when compared with the twice-daily LABAs.[52–55] In a noninferiority study directly comparing indacaterol to tiotropium for 12 weeks,[56] both drugs showed similar efficacy in terms of increased trough FEV_1. Indacaterol also had a significantly greater bronchodilator effect than tiotropium within 1 hour from the first dose. Indacaterol treatment is accompanied by significant reductions in dyspnea and as-needed albuterol use. Health status generally improved with decreases from baseline St George's Respiratory Questionnaire (SGRQ) score greater than four units.[57] Indacaterol also has been shown to reduce COPD exacerbations[57] and improve exercise endurance time as compared to placebo.[58] Compared to tiotropium monotherapy, adding indacaterol with tiotropium improved the bronchodilator effect and lung deflation.[52]

The safety of indacaterol has been thoroughly studied;[52,53,56,59,60] its major side effects include tremor and tachycardia, but it appears to have low arrhythmogenic potential.[51,59,61] Indacaterol has been approved in more than 50 countries for the maintenance treatment of COPD. In 2009, indacaterol (Onbrez®) was approved in the EU at doses of 150 µg and 300 µg inhaled once daily delivered via a novel dry-powder inhaler (Breezhaler®). In the US, the US FDA had issues with indacaterol dosing,[62] but it approved indacaterol (Arcapta™) in July 2011 at a dose of 75 µg once daily, delivered by a dry-powder inhaler (Neohaler™).

Vilanterol

Vilanterol trifenatate is a novel LABA anticipated for inhaled once-daily administration in combination with an ICS fluticasone furoate (Relvar® Ellipta®, Breo® Ellipta®, Revinity® Ellipta®) or in combination with the LAMA umeclidinium (Anoro® Ellipta®).[63–65] The pharmacokinetics of vilanterol is consistent with a dose-dependent, rapid-onset, 24-hour lasting bronchodilator in patients with COPD. It is a highly selective LABA with affinity toward β-2 adrenoreceptors similar to salmeterol, but with a significantly faster onset of action.[66] The tolerability profile is similar to placebo.[63,67] A recently published randomized control 12-week study compared the cardiac safety of this combination to tiotropium alone.[68] The results showed no difference in aortic pulse wave velocity, a predictor of cardiovascular events and mortality.

Combination therapy with both fluticasone and umeclidinium was shown to improve lung function and reduce exacerbations when compared to monotherapy.[69–71] Vilanterol has received approval by the US FDA for the maintenance treatment of COPD in the form of a fixed-combination therapy only.[72]

Olodaterol

Olodaterol is another novel LABA with dose-dependent bronchodilator effects lasting up to 24 hours.[67,73,74] Furthermore, it protects against methacholine-induced bronchoconstriction

in patients with intermittent asthma for up to 32 hours after administration of a single dose.[67,75] In a 48-week study of moderate to very severe COPD,[76] olodaterol once daily was compared to both formoterol twice daily and placebo. Olodaterol and formoterol improved FEV_1 when compared to placebo, but olodaterol also showed significant improvements in reported symptoms.[76] Along with tiotropium, olodaterol has been investigated as a potential agent that counters the detrimental effect of the Th-17 immune response in the development of COPD.[77] Adverse effects reported with olodaterol were comparable with placebo in two clinical trials.[67,78] Olodaterol (Striverdi®) was initially designed for use in combination with tiotropium to provide added benefit for patients with COPD. It is currently approved as a monotherapy in over 30 countries and it was approved by the US FDA in August 2014 for the maintenance treatment of COPD at a dose of 5 μg once daily, delivered by a soft-mist inhaler (Respimat®).

Abediterol

Early clinical trials indicate that abediterol may be a potent, rapid, and long-acting bronchodilator.[79] Abediterol elicits bronchodilation 5 minutes after dosing, which is faster and longer lasting than salmeterol 50 μg twice daily.[67,80] The high level of β-2 adrenoreceptor subtype selectivity may account for its comparable cardiovascular safety and tolerability profile when compared to placebo.[63,81,82]

New LAMA-LABA combination therapies

Background

Combination therapy involving two long-acting bronchodilators with differing mechanisms of action has been recommended in patients whose COPD is not well controlled with one drug alone.[1,12] LAMA and LABA combinations show synergistic bronchodilator effects at doses used for monotherapy.[83,84] In addition, fixed-dose combination LAMA-LABA regimens may be more convenient and lead toward better adherence by patients.[85]

Umeclidinium and vilanterol

Umeclidinium/vilanterol (Anoro® Ellipta®) is a once-daily LAMA-LABA combination drug that was shown to improve lung function compared with vilanterol or tiotropium alone in patients with COPD.[70] In recent randomized controlled trials, its use has led to statistically significant improvements in FEV_1, health status, and dyspnea scores during the 24-week period when compared to placebo and to umeclidinium and vilanterol monotherapies.[69,85] This combination was proven to be safe and well tolerated,[86–88] and it has become the first fixed-dose combination LAMA-LABA product approved by the US FDA for the maintenance treatment of COPD.

Glycopyrronium and indacaterol

In a recently published trial,[89] the glycopyrronium/indacaterol combination was compared to its individual components (glycopyrronium and indacaterol) and tiotropium for the treatment of moderate to severe COPD. The results revealed better efficacy with the inhaled combination therapy when compared with glycopyrronium or tiotropium alone. Analyzing the efficacy compared to indacaterol, two studies[90,91] grouped together, including 1,399 patients with moderate to severe COPD, revealed significantly improved FEV_1 in the glycopyrronium/indacaterol group compared to indacaterol alone. The overall incidence of adverse events was similar across both treatment groups.[92]

Glycopyrronium/indacaterol (Ultibro® Breezhaler®) was the first-in-class once-daily dual bronchodilator approved in Europe in 2013 for use by patients suffering from COPD.

Tiotropium and olodaterol

The combination of tiotropium and olodaterol is under development as a soft-mist inhaler. Results from a recent randomized, double-blind, parallel-group, multicenter, Phase III trial comparing the fixed-dose combination inhaler to its monocomponents revealed significant improvements in FEV_1 and SGRQ score.[74] Patients enrolled in the study had moderate to very severe COPD and were followed for 1 year. The significant improvement in SGRQ score was only seen with the tiotropium/olodaterol dosing of 5/5 μg daily.

Aclidinium and formoterol

Aclidinium bromide/formoterol fumarate (Duaklir Pressair) is an investigational fixed-dose combination of two approved long-acting bronchodilators given twice daily. A Phase III clinical trial[93] combining formoterol fumarate and aclidinium bromide resulted in significantly improved FEV_1 through a 24-week period. There were no significant differences in health status, as reflected by health-related quality of life scores and rate of exacerbations between the fixed-dose combination, aclidinium bromide, formoterol fumarate, and placebo.

Glycopyrrolate and formoterol

The formoterol/glycopyrrolate (PT003) fixed-dose combination delivered via a pressurized hydrofluoroalkane

is currently in Phase III trials for use in moderate to very severe COPD in the US and Europe.[94–99] Recent studies reported improvements in FEV_1 area under the curve from 0 hours to12 hours versus monotherapy with glycopyrrolate, formoterol, or tiotropium, and in inspiratory capacity versus tiotropium monotherapy.[83,100,101]

New LABA-ICS combination therapies

Background

Evidence suggests that LABA and ICS have synergistic effects in the airways of people living with COPD. ICS can potentiate LABA effects by preventing the reduction of cell surface-expressed β-receptors that occurs with severe airway inflammation. Concurrently, LABAs may have steroid-sparing, anti-inflammatory, and antiproliferative properties.[102] It has been postulated that the simultaneous inhalation of both drugs via a single device in a single breath may maximize the drug codeposition and facilitate greater interaction between the ICS and the LABA.[103] In a recent meta-analysis by the Cochrane network,[104] the ICS/LABA combination demonstrated the most significant improvement in both the SGRQ and FEV_1 compared to placebo. In addition, combination therapy showed improvement over LAMA, LABA, and ICS therapy alone.[104] Recently, a published review of comparative safety in inhaled COPD regimens found that ICS/LABA had the lowest risk of mortality when compared with placebo, tiotropium, or LABA alone.[105] There are now new LABA-ICS fixed-dose combinations to add to the previously available twice-daily combinations, which have included fluticasone/salmeterol (Advair), budesonide/formoterol (Symbicort), and mometasone/formoterol (Dulera).

Vilanterol and fluticasone

Vilanterol/fluticasone furoate (Relvar®, Breo®, Revinty®) is a fixed-dose combination of ICS and LABA for once-daily administration via a dry-powder inhaler (Ellipta®), and this has recently been approved by the US FDA for patients suffering from COPD.[106] In comparison to twice-daily fluticasone propionate/salmeterol, fluticasone furoate/vilanterol once daily has shown trends for improved FEV_1, but without clinical significance in multiple 12-week trials.[107] Compared to vilanterol alone, the combination regimen showed significantly fewer moderate to severe COPD exacerbations.[71] Serious adverse effects are similar to the fluticasone propionate/salmeterol inhaler.[107] In comparison to vilanterol only, fluticasone furoate/vilanterol led to an increased risk of pneumonia, fractures, and mortality.[71] A key advantage is not evident through its efficacy, but in its once-daily dosing, which offers greater convenience to patients and ideally improves compliance.

Indacaterol and mometasone

The combination of indacaterol acetate and mometasone furoate (QMF149; Novartis International AG, Basel, Switzerland) is also in the late stages of development.[108] Its safety, tolerability profile, and effect on lung function compared to placebo in airway diseases have shown promising results.[74,109,110]

Formoterol and ciclesonide

The combination of formoterol and ciclesonide (Alvesco Combo) has been investigated in moderate asthma patients. In a Phase II trial,[111] formoterol/ciclesonide was found to be noninferior to fluticasone/salmeterol in terms of both efficacy and tolerability. Studies investigating its use in COPD are still lacking.

Formoterol and fluticasone

The combination of fluticasone propionate/formoterol (Flutiform®, Abriff®, or Iffeza®) in a single inhaler provides potent anti-inflammatory activity of fluticasone propionate and rapid onset of action of the β2-agonist formoterol.[112] It has been marketed for use in asthma in Europe and Japan, and it has been in Phase III trials for its use in moderate to severe COPD. The efficacy of fluticasone/formoterol in patients with asthma was shown to be noninferior to that of fluticasone/salmeterol or budesonide/formoterol with a tolerability profile generally similar to that of these two combinations.[113]

Triple LABA-LAMA-ICS therapy

Triple therapy consisting of LABA, LAMA, and ICS has been investigated showing benefits in comparison to LABA-ICS or LAMA alone.[114–122] Tiotropium added to the salmeterol/fluticasone combination did not lead to fewer exacerbations in comparison to the three component parts alone, but it did improve lung function and disease-specific quality of life compared to tiotropium monotherapy.[122] Triple therapy was associated with a 40% reduction in mortality compared with ICS/LABA in a retrospective analysis among veterans with COPD.[117] Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) update in 2013, patients classified as group D should be prescribed with ICS combined with a LABA or LAMA, "with some evidence for triple therapy".[1] Currently, there are several inhalers containing LAMA-LABA-ICS combinations undergoing early phase

clinical trials, including glycopyrronium/formoterol fumarate/budesonide inhalation aerosol (BGF MDI, PT010), umeclidinium/vilanterol/fluticasone inhaler, and tiotropium/formoterol furoate/ciclesonide inhaler (Triohale).

Dual muscarinic antagonist-β2-agonists (MABAs)

MABAs, which can deliver a fixed ratio of muscarinic antagonist and β_2-agonist to the whole lung with a single pharmacokinetic profile, comprise an attractive idea that could further facilitate the application of "triple therapy".[83] One of furthest developed MABAs, GSK961081, has demonstrated effective bronchoprotection in vivo as proof of concept, and it is still in early clinical trials.[123]

Oral medications

Roflumilast

Oral phosphodiesterase (PDE) inhibitors have been shown to relax smooth muscle, suppress the activation of inflammatory cells, and modulate the activity of pulmonary nerves.[124] Xanthines such as theophylline are nonselective PDE inhibitors, and they were among the first agents used in the treatment of COPD. Due to a very narrow therapeutic window and their severe adverse effects, their popularity decreased over past decades as new and safer agents became available. In search for more specific PDE inhibitors, the development of PDE3 and/or PDE4 inhibitors, as well as the enzymes responsible for metabolizing cyclic adenosine monophosphate in the airway and pulmonary smooth muscle, showed promise in the treatment of respiratory diseases like asthma and COPD.[125,126] Cilomilast is a second-generation PDE4 inhibitor that had initially shown improvements in efficacy endpoints and provided evidence for an anti-inflammatory mechanism of action, but Phase III studies failed to definitively confirm these findings, which led to the termination of the development of cilomilast.[127] Roflumilast (Daliresp®) is a newly approved selective PDE4 inhibitor for the treatment of severe COPD associated with chronic bronchitis and frequent exacerbations.[128] It is an oral once-daily drug, currently available in 500 μg tablets. Roflumilast improved FEV_1 to a degree compared to that of ICSs in clinical trials,[129–131] but its effects on the rates of exacerbation and quality of life measures have not been as consistent.[128] The safety profile of roflumilast, while improved compared to nonspecific PDE inhibitors, still leads to its recommended use only in advanced COPD as an add-on therapy. Its side effects are generally tolerable, but significant weight loss, diarrhea, and psychiatric symptoms remain reasons for the cautious use of this medication.[128,132,133]

Azithromycin

Multiple studies have confirmed the correlation between lower airway bacterial colonization and acute exacerbations of COPD.[134–136] Furthermore, a classic study showed improved outcomes after antibiotic treatment in patients with two of the three classic symptoms (increased dyspnea, increased sputum volume, and sputum purulence).[137] A patient who continues to have frequent acute exacerbations despite guideline-based treatment is a potential candidate for prophylactic use of azithromycin. In addition to its antimicrobial efficacy, azithromycin may have anti-inflammatory and immune-modulating effects.[138] Several prospective studies focused on a long-term use of azithromycin (azithromycin 500 mg versus placebo three times a week for 12 months, and azithromycin 250 mg daily versus placebo). These studies revealed significant reductions in acute exacerbations, hospitalizations, and length of hospital stay in patients with severe COPD.[139–142] In a large, placebo-controlled, randomized trial among selected patients with COPD,[143] azithromycin 250 mg taken daily for 1 year, when added to usual treatment, decreased the frequency of exacerbations by 27% and improved quality of life. Of particular importance for patients with frequent exacerbations (three or more exacerbations per year), maintenance treatment with azithromycin significantly decreased the exacerbation rate compared with placebo.[141] A recently published study evaluated daily azithromycin use for the prevention of acute exacerbations of COPD.[144] This study showed prolonged time to first exacerbation in older patients (>65 years) and those with GOLD spirometric stages 3 and 4. However, there was no effect on exacerbations in active smokers.

One of the shortcomings of azitrhomycin therapy is that, although it is less likely to become colonized with respiratory pathogens, persons suffering from COPD are more likely to become colonized with macrolide-resistant organisms.[143] Other serious concerns include three major categories of adverse effects that may be anticipated with the year-long use of azithromycin. These include cardiac toxicity and QT interval prolongation,[145] ototoxicity,[143] and drug–drug interactions from CYP3A4 iso-enzyme inhibition.[138] Collectively, these concerns are enough to promote controversy regarding treatment recommendations.[146–153] The GOLD report[1] even states that "a recent trial of daily azithromycin showed efficacy on exacerbation end points; however, treatment is not recommended because of an unfavorable balance between benefits and side effects".

Moxifloxacin

In a randomized controlled trial, pulsed moxifloxacin 400 mg taken orally once daily for 5 days, repeated every 8 weeks for 48 weeks, significantly reduced COPD exacerbations by

25% (P=0.046). A greater reduction in COPD exacerbations (a 45% reduction) was seen in patients with purulent or mucopurulent sputum at baseline.[154] This study further illustrates the efficacy of antimicrobial therapy in a selected population of patients with COPD.

Simvastatin

Another randomized controlled trial investigated the effects of statin therapy on the frequency of COPD exacerbations.[155] A total of 885 participants with COPD were involved in this study. Simvastatin 40 mg or placebo was taken orally once daily, for between 12 months and 36 months. However, the rate of exacerbations was not different between the two groups.

New therapy in development

Although therapeutic advances in the treatment of COPD and emphysema are promising, our understanding of the pathophysiology is incomplete. Given the complexity of COPD, there are multiple potential targets for the treatment of this disease and for prevention of its progression.

Novel inhaled dual PDE3 and PDE4 inhibitors, such as RPL554 and the PDE4 inhibitor CHF6001, are being investigated for their potential bronchodilator and anti-inflammatory effects in asthma and COPD. In multiple functional assays, CHF6001 was shown to be more potent than the previously described PDE4 inhibitors, such as roflumilast (UK-500,001) and cilomilast.[156] In four exploratory studies, inhaled RPL554 was proven to be an effective and well-tolerated bronchodilator and anti-inflammatory drug.[157] Several early clinical studies of short duration and small sample sizes showed promising safety profiles and bronchodilator response of these compounds with comparable efficacy to salbutamol.[157,158]

A novel macrolide/fluoroketolide, solithromycin (CEM-101), which is currently being investigated in the treatment of community-acquired pneumonia, has shown better anti-inflammatory profiles compared with the currently available macrolides, and it may be a promising anti-inflammatory and antimicrobial drug for the treatment of COPD in the future.[159]

N-acetylcysteine (NAC) is one of the most widely used and tested antioxidants. This drug has been shown to reduce bronchial hypersecretion and has been used as a mucolytic for many years.[160–163] Only recently have studies addressed its effects more scientifically; it has reportedly slowed the decline in FEV_1 and led to a reduction in the number of COPD exacerbations.[164–167]

Antagonists of the human CXCR2 receptors may affect neutrophil trafficking, and they have been investigated in COPD. One of the CXCR2 antagonists, MK-7123, showed improved FEV_1 in comparison to placebo in patients with COPD, and it has also been investigated in Phase II clinical trials.[168]

Other potential therapeutic targets include the regulation of signaling pathways – for example, by p38 mitogen-activated protein kinase (p38 MAPK). p38 MAPK inhibitors have shown favorable anti-inflammatory properties and have the potential to reverse corticosteroid insensitivity in COPD.[169] Early clinical trials of an oral p38 MAPK inhibitor (PH-797804) showed favorable tolerability, improved FEV_1, and improved baseline dyspnea index compared with placebo.[169,170] Nevertheless, Phase II trials of this agent have recently been discontinued.[171] Another potent oral p38α/β MAPK inhibitor, losmapimod (GW856553X), is in a Phase II human clinical trial for the treatment of COPD.[172] Also, acumapimod is an orally delivered p38 MAPK inhibitor that remains in active development.[173] Inhaled delivery of p38 MAPK inhibitors may enhance p38 inhibition in the lung while reducing unwanted systemic effects. The efficacy and safety of two inhaled p38 MAPK inhibitors, RV-568 and PF-03715455, are currently being evaluated in clinical trials.[173]

Based on the hypothesis that inflammation in COPD is a consequence of a protease and antiprotease imbalance, antagonizing matrix metalloproteinases (MMP) with selective MMP inhibitors offers a potential solution.[174] A dual MMP9–MMP12 inhibitor (AZ11557272) was shown to prevent emphysema, small airway fibrosis, and inflammation in guinea pigs that were exposed to cigarette smoke over a 6-month period,[175] but its clinical development has recently been stopped. Another potent and reversible inhibitor of human MMP9 and MMP12 (AZD1236) administered orally has failed biomarker endpoints for COPD, despite initial promising results, so its further development has also been aborted.

Emerging anticytokine therapies require careful selection of patients with COPD.[176] Benralizumab and mepolizumab are humanized monoclonal antibodies directed at the alpha subunit of the interleukin (IL)-5 receptor (IL-5Rα). Both drugs are currently in Phase III development for both COPD and severe asthma.[177–188] Benralizumab was shown to reduce COPD exacerbations and improve other symptoms of COPD in certain patient groups.[189] Patients with higher baseline levels of blood eosinophils who were treated with benralizumab showed greater improvements in COPD symptoms, including exacerbation rate, lung function, and disease-specific health status, as measured by the SGRQ-COPD (SGRQ-C) when compared with placebo-treated subjects.[189]

Antihuman IL-17R antibodies (such as ixekizumab, brodalumab, and ustekinumab) are currently available for

clinical studies in COPD, having recently been reported in a study of patients with asthma.[190]

The phosphoinositide 3-kinases (PI3K) are a family of proteins that control a wide variety of intracellular signaling pathways and may be attractive in the management of COPD since they may restore steroid effectiveness under conditions of oxidative stress.[191] PI3Kδ inhibition with agents such as GSK2269557 may also prevent recruitment of inflammatory cells, including T-lymphocytes and neutrophils as well as the release of proinflammatory mediators such as cytokines, chemokines, reactive oxygen species, and proteolytic enzymes.[65,191]

Soluble epoxide hydrolase inhibitors may also play a pharmacological role in the future treatment of COPD. Treatment with soluble epoxide hydrolase, such as t-TUCB – which is in its early stages of development – may increase fatty acid epoxides and indirectly reduce the production of Th1 cytokines and proinflammatory lipid mediators, while minimizing airway obstruction and reducing weight loss in animal models of COPD.[192]

Palovarotene©, an orally active, gamma-selective retinoid agonist has been studied in patients with emphysema secondary to alpha-1-proteinase inhibitor deficiency as a model population for smoke-induced emphysema. Early clinical trials showed beneficial effects in multiple functional lung parameters,[193,194] but further development as a COPD treatment has recently been abandoned.

Ongoing Phase I clinical trials of patients with advanced pulmonary emphysema treated with autologous infusion of bone marrow mononuclear cells have shown promising results with improved spirometry, slowed progression of emphysema, and improved quality of life without significant adverse effects.[195]

Conclusion

The availability of increasing numbers of therapeutic agents brings new optimism in the management of patients with COPD. The short-action inhaled bronchodilators will continue to be necessary for the relief of intermittent symptoms, or as rescue medication in event of breakthrough symptoms. Short-acting muscarinic antagonists and short-acting beta agonists can be prescribed as metered-dose inhalers (hydrofluoroalkane) or as soft-mist inhaler formulations. Novel long-acting inhaled bronchodilators are suitable as maintenance (daily) treatment in patients with persistent symptoms who find the need to use any type of inhaler on a daily basis. The choice includes LAMA, LABA, or LAMA-LABA combination therapy. Patients with uncontrolled disease despite taking both LAMA and LABA should be referred for specialist evaluation in the hopes of identifying a specific COPD phenotype that might be suitable for additional pharmacotherapy. Such phenotypes might include the asthma–COPD overlap syndrome in which triple-inhaler therapy can be considered through the addition of an ICS. Frequent exacerbators, those with lower airway bacterial colonization and those with coexistent bronchiectasis, could be considered for oral treatment with a selective PDE4 inhibitor or long-term antibiotic prophylaxis. Future studies may reveal the necessity to recognize COPD as a disease with many manifestations requiring a specific and tailored therapeutic approach for each of its clinical phenotypes.

Disclosure

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