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Newer Therapies in COPD

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute significantly to the overall severity in individual patients. COPD affects nearly 8% of the world's population concerning 160 million people. COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. The prevalence of COPD is directly related to the prevalence of tobacco smoking (being the strongest risk factor ever known), although, outdoor, occupational and indoor air pollution are also major COPD risk factors. The burden of COPD is likely to increase in the coming decades due to continued exposure to COPD risk factors and due to increased life expectancy. A varying degree of inhalational injury & genetic susceptibility lead to phenotypic heterogeneity - a hallmark of COPD.

THERAPEUTICS IN COPD

The management of COPD encompasses preventative measures, pharmacological treatment, nonpharmacological management, and surgical options in appropriate patients (Table 1). Smoking cessation is the only intervention established to influence the natural history of COPD. Various forms of nicotine replacement therapies are available for the patients with difficulties in smoking cessation like withdrawal symptoms. In some countries, influenza and pneumococcal vaccinations are also recommended as a preventive therapy as a part of National Guidelines.

Table 1: Management of COPD

Management subtype	Modality
Preventative	Smoking cessation Avoidance of toxic exposures Improvement in airways pollution
Pharmacological	Established drugs recommended by guidelines Newer drugs
Nonpharmacological	Supplemental oxygen Pulmonary rehabilitation
Surgical	Lung volume reduction surgery, Endoscopic lung volume reduction Lung transplantation.

PHARMACOTHERAPIES ESTABLISHED IN VARIOUS GUIDELINES

Primary intention of any pharmacological therapy in COPD is to reduce symptoms, decrease the frequency and severity of exacerbations, and improve health related quality of life status and exercise tolerance. COPD medicines available presently have not been conclusively shown to modify the long-term decline in lung function that is the hallmark of this disease. The recommended medications as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines (2016) are mentioned in tabular form in Table 2.

Inhaled bronchodilator therapy is uniformly accepted across numerous Guidelines as a first-line therapy for symptomatic COPD, in contrast to asthma where the anti-inflammatory properties of inhaled corticosteroids warrant them as the first-line therapy. Inhaled bronchodilators in COPD have been shown to improve dyspnea, exercise performance, and overall health status. They are also found to be useful in reducing acute COPD exacerbations. The improvement in exercise performance carries potential benefit of an active life often debilitated in severe COPD patients. Exacerbations are uncomfortable and distressing to people with COPD, and often reduce health related quality of life. A reduction of exacerbations is also having significant impact on health status, health care expenditure, exercise performance, and survival. The accumulated data across various studies suggests the beneficial effect of bronchodilator therapy in term of disease progression in COPD possibly due to a significant reduction in exacerbations thereby portending a mortality benefit. Inhaled corticosteroids are recommended in severe persistent COPD (forced expiratory volume in 1 second [FEV1] < 50% of predicted). They are usually combined with a LABA as additional benefits include an improvement in pulmonary function and reduction in frequency of exacerbation; it is hypothesized that a reduction in airway inflammation and bronchial wall edema account for pulmonary function improvement.

Group wise treatment in COPD as recommended by GOLD Guidelines is shown in Table 3. The selection of a particular drug amongst its class is largely guided by

Table 2: GOLD recommended COPD Medications
Beta2-agonists
Short-acting beta2-agonists
Fenoterol
Levalbuterol
Salbutamol (albuterol)
Terbutaline
Long-acting beta2-agonists
Formoterol
Arformoterol
Indacaterol
Olodaterol
Salmeterol
Tulobuterol
Anticholinergics
Short-acting anticholinergics
Ipratropium bromide
Long-acting anticholinergics
Aclidinium bromide
Glycopyrronium bromide
Tiotropium
Umeclidinium
Combination short-acting beta2-agonists & Anticholinergic in one inhaler
Combination long-acting beta2-agonist & anticholinergic in one inhaler
Methylxanthines
Aminophylline
Theophylline (SR)
Inhaled corticosteroids
Beclomethasone
Budesonide
Fluticasone
Combination long-acting beta2-agonists & corticosteroids in one inhaler
Systemic corticosteroids
Prednisolone
Methyl Prednisolone
Phosphodiesterase-4 inhibitors
Roflumilast

the cost, availability in the local market and acceptance by the patient in term of adverse drug reactions/ drug interactions.

NEWER THERAPIES FOR COPD

Our understanding of pathophysiology of COPD has reached to new heights during last couple of decades, and as a result new potential targets for the management of this disease and for prevention of its progression have been identified. Many of new molecules are under different trial phases and yet to achieve desired acceptance and recommendations. Table-4 enlists some of these promising molecules.

New Long-Acting Long-Acting Muscarinic Antagonists (LAMA)

Aclidinium

Aclidinium bromide has been approved in United States and Europe since 2012 for maintenance therapy of COPD. The clinical trials have observed aclidinium to significantly improve pulmonary function (FEV1), dyspnea, and health status. It is formulated as dry powder and delivered via a multidose inhaler. The drug was well tolerated in patients with COPD due to rapid plasma hydrolysis, which might account for reduced systemic exposure and a lower reported incidence of anticholinergic adverse effects.

Glycopyrronium

Glycopyrronium bromide has a relative kinetic selectivity for the M3 versus M2 receptors that facilitates airway smooth muscle relaxation. It has proven bronchodilator effects, and, in comparison with tiotropium, has shown a faster onset of action and achieves a significantly higher FEV1. Glycopyrronium significantly reduces the risk of COPD exacerbations and also improves exercise endurance time. Glycopyrronium was approved in the EU in 2012 and is delivered via a dry-powder inhaler.

Umeclidinium

Umeclidinium bromide has been found to be suitable both as monotherapy and in combination for maintenance use in COPD. Sustained bronchodilatation over a period of 24-hour permits once a day therapy. It improves pulmonary function (weighted mean FEV1), breathlessness, and health status. Umeclidinium has been approved by the US FDA since April 2014 as a monotherapy with a dose of 62.5 μg once daily. It is formulated as a dry powder to be delivered via an inhaler.

New Long-Acting Beta2-Agonist Monotherapy

Indacaterol

Indacaterol has a stronger affinity for β-2 adrenergic receptors and its proven advantages include longer duration of bronchodilatation and faster onset of action with improved cardiovascular safety profile when compared to salmeterol. Indacaterol has been shown to improve health status and exercise enduration time and to reduce COPD exacerbations. The addition of indacaterol to tiotropium synergistically potentiates bronchodilator effect of later. It appears to have low arrhythmogenic potential. Presently, indacaterol has been approved in more than 50 countries for the maintenance treatment of COPD. It was approved in the EU in 2009 and in US in 2011. The drug is currently available in India as monotherapy as well as a combination with Glycopyrronium.

Vilanterol

Vilanterol trifenatate has a preferential affinity to β-2 adrenoreceptors similar to salmeterol, but with a significantly faster onset of action and a dose-dependent

Table 3: Group wise treatment in COPD as recommended by GOLD Guidelines

COPD Patient Groups →	Group A	Group B	Group C	Group D
Recommended first choice of treatment	Short-acting anticholinergic as needed or Short-acting beta2-agonist as needed	Long-acting anticholinergic or Long-acting beta2-agonist	Inhaled corticosteroid + long-acting beta2-agonist or Long-acting anticholinergic	Inhaled corticosteroid + long-acting beta2-agonist and/or Long-acting anticholinergic
Alternative treatment	Long-acting anticholinergic or Long-acting beta2-agonist or Short-acting beta2-agonist and short-acting anticholinergic	Long-acting anticholinergic and long-acting beta2-agonist	Long-acting anticholinergic and long-acting beta2-agonist or Long-acting anticholinergic and phosphodiesterase-4 inhibitor or Long-acting beta2-agonist and phosphodiesterase-4 inhibitor	Inhaled corticosteroid + long-acting beta2-agonist and long-acting anticholinergic or Inhaled corticosteroid + long-acting beta2-agonist and phosphodiesterase-4 inhibitor or Long-acting anticholinergic and long-acting beta2-agonist or Long-acting anticholinergic and phosphodiesterase-4 inhibitor
Other options	Theophylline	Short-acting beta2-agonist and/or Short-acting anticholinergic Theophylline	Short-acting beta2-agonist and/or Short-acting anticholinergic Theophylline	Carbocysteine N-acetylcysteine Short-acting beta2-agonist and/or Short-acting anticholinergic, Theophylline

and 24-hour lasting bronchodilatation in patients with COPD. Combination therapy with both fluticasone and umeclidinium has been shown to improve lung function and reduce exacerbations when compared to monotherapy. In US, vilanterol is approved only as a fixed-combination therapy for the maintenance treatment of COPD.

Olodaterol

Olodaterol is reported to have a dose-dependent bronchodilator action lasting up to 24 hours. Olodaterol and formoterol improved FEV1 when compared to placebo; additionally, olodaterol also improved COPD reported symptoms. Studies indicate olodaterol to have a potential role to counter the detrimental effect of the Th-17 immune response in the development of COPD. Olodaterol is a relatively safe drug, approved as maintenance treatment in COPD and currently permitted as a monotherapy in over 30 countries.

Abediterol

Early clinical trials indicate that abediterol to be a potent bronchodilator with rapid onset and long lasting action. A higher selectivity to β-2 adrenoreceptors subtype permits better cardiovascular safety and tolerability profile.

NEW COMBINATION THERAPY

New LAMA + LABA Combination Therapy

During the last decade, various combinations of new LAMA and new LABA have been studied; many of them

Table 4: New COPD Therapies

Group	Drugs	Group	Drugs
New LAMA monotherapy	Aclidinium Glycopyrronium Umeclidinium	New LABA+ICS Combination	Vilanterol & Fluticasone Indacterol & Mometasone Formetrol & Ciclesonide Formetrol & Fluticasone
New LABA monotherapy	Indacterol Vilanterol Olodaterol Abediterol	Triple drug LABA+LAMA+ ICS Combination	Tiotropium + Salmetrol + fluticasone Glycopyrronoum + Formoterol + Budesonide
New LAMA+ LABA Combination	Umeclidinium & Vilanterol Glycopyrronium & Indacterol Tiotropium & Olodetrol Aclidinium & Formoterol Glycopyrrolate & Formoterol	Oral Medications	Roflumilast Simvastatin N-acetylcysteine

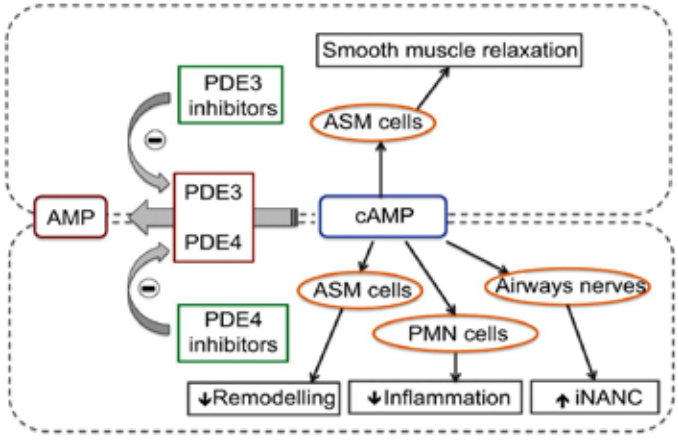

Fig. 1: Role of phosphodiesterase (PDE) inhibitors in COPD

were found to be promising and approved in various countries. Umeclidinium and vilanterol combination has been approved in US and European Union for GOLD groups C and D. The combinations of glycopyrronium and indacaterol as well as that of aclidinium and formoterol have been permitted in European Union for GOLD groups C and D.

New LAMA + ICS Combination Therapy

The combinations of LABA and ICS have been reported to have synergistic effects. ICS potentiates LABA effects by preventing the reduction of cell surface expressed β-receptors - a hallmark of airway inflammation. On the other hand, LABA has steroid-sparing, anti-inflammatory and antiproliferative properties. The Cochrane meta-analysis suggests ICS/LABA combination to have significant improvement in both the SGRQ and FEV1 compared to LAMA, LABA, and ICS therapy alone. The combination of vilanterol and fluticasone has been permitted in US and European Union for GOLD groups C and D. Formoterol and ciclesonide combination was found to be noninferior to fluticasone & salmeterol in terms of both efficacy and tolerability. Formoterol and fluticasone has been approved in Japan and European Union for GOLD groups C and D.

Triple LABA-LAMA-ICS therapy

Triple therapy has been observed to be associated with a 40% reduction in mortality compared with ICS/LABA combination and improve lung function and health related quality of life compared to tiotropium monotherapy. GOLD 2013 update recommends the use of triple therapy in patients with COPD group D. Currently, there are several inhaled therapy containing LAMA + LABA + ICS combinations undergoing clinical trials, including glycopyrronium + formoterol + budesonide, umeclidinium + vilanterol + fluticasone, and tiotropium + formoterol + ciclesonide.

Phosphodiesterase Inhibitors

Roflumilast- Oral Phosphodiesterase Inhibitors

Oral phosphodiesterase (PDE) inhibitors have been shown to suppress the activation of inflammatory cells, modulate the activity of pulmonary nerves, and relax smooth muscle (Figure-1). Roflumilast has been observed to improve FEV1 comparable to ICSs in clinical trials, but not found to be consistently efficacious in term of reduction in frequency of exacerbation and quality of life. Roflumilast as a selective PDE4 inhibitor is recommended in US and European Union for treatment in severe COPD associated with frequent exacerbations. The safety profile of roflumilast still limits its use only in advanced COPD as an add-on therapy.

Inhaled Phosphodiesterase Inhibitors

Dual PDE3 and PDE4 inhibitors, such as RPL554 and the PDE4 inhibitor CHF6001, are under trial phase in asthma and COPD. CHF6001 was shown to be more potent than roflumilast. In four exploratory studies, inhaled RPL554 was found to be an effective and well-tolerated bronchodilator as well as anti-inflammatory drug.

TARGETED DRUG THERAPY IN COPD

CXCR2 Antagonists

Antagonists of the human CXCR2 receptors target neutrophil trafficking in COPD inflammatory pathway. MK-7123, a CXCR2 antagonist, is being investigated in Phase II clinical trials and has shown significant improvement in FEV1 compared to placebo in patients with COPD.

P38 Mitogen-Activated Protein Kinase (P38 MAPK) Inhibitors

P38 mitogen-activated protein kinase pathway involves a signaling cascade controlling cellular responses to cytokines and stress. Table-5 represents the various molecules under study. The molecule PH-797804 studied had shown improvements in dyspnea symptom index and FEV1. Losmapimod (GW856553X) the other potent oral p38α/β MAPK inhibitor, is in a phase II clinical trial for the treatment of COPD.

The efficacy and safety of two inhaled p38 MAPK inhibitors, RV-568 and PF-03715455 are under various phases of clinical trials. Inhaled delivery of p38 MAPK inhibitors may enhance p38 inhibition in the lung while reducing unwanted systemic effects.

Selective Matrix Metalloproteinases (MMP) Inhibitors

As we know COPD is an inflammatory disorder in which protease and antiprotease imbalance plays an important role, antagonizing matrix metalloproteinases (MMP) with selective MMP inhibitors provided an option to revert back to this fine balance. The search for ideal drug in this group goes on; some of the studied molecules are listed in Table-6.

Table 5: P38 Mitogen-Activated Protein Kinase (P38 MAPK) Inhibitors

Drug	Group	Present status
PH-797804	Oral p38 MAPK inhibitor	Phase II trials of this agent have recently been discontinued.
GW856553X/ Osmapimod	Oral p38α/β MAPK inhibitor	Phase II human clinical trial
Acumapimod	Orally p38 MAPK inhibitor	Active development
RV-568	Inhaled p38 MAPK inhibitors	Evaluated in clinical trials
PF-03715455	Inhaled p38 MAPK inhibitors	Evaluated in clinical trials

Humanized monoclonal antibodies targeted to alpha subunit of the interleukin (IL)-5 receptor (IL-5Rα)

The interlukin (IL) -5 receptor is composed of an α and a βc chain, α subunit has affinity for IL-5 only whereas βc subunit has affinity for IL-5, IL-3 and Granulocyte-macrophage Colony-stimulating Factor (GM-CSF). Humanized monoclonal antibodies targeted to alpha subunit of the interleukin (IL)-5 receptor (IL-5Rα) selectively blocks IL-5 (Table 7). This action is particularly beneficial in management of asthmatic inflammation as well as COPD exacerbations. Soluble IL-5Rα is also found to be increased during virus-induced COPD exacerbations.

Antihuman IL-17R Antibodies

Interlukin (IL) -17A has been found to induce neutrophilic inflammation by releasing CXCL1, CXCL8 and GM-CSF from airway epithelial cells and smooth-muscle cells. IL-17A can induce IL-6 expression in bronchial epithelial cells and fibroblasts. IL-17A is involved in human airway smooth-muscle contraction. Th17 cells also mediate glucocorticoid-resistant airway inflammation and airway hyperresponsiveness. Antihuman IL-17R antibodies including **Ixekizumab**, **Brodalumab** and **Ustekinumab** are under trial for possible clinical efficacy in asthma and COPD.

Phosphoinositide 3-kinases (PI3K) Inhibitors

The phosphoinositide 3-kinases (PI3K) are a family of proteins that are involved in the control of intracellular signaling pathways. Phosphoinositide 3-kinases inhibitors prevent recruitment of inflammatory cells including t-lymphocytes and neutrophils, prevent release of proinflammatory mediators, and also may restore steroid effectiveness. One molecule with promising phosphoinositide 3-kinases inhibitor property is GSK2269557, which is being further evaluated.

CONCLUSIONS

During last decade, a large number of molecules have been investigated for possible potential to be used in treatment of COPD; increasing numbers of therapeutic agents may appear confusing but brings new optimism for COPD management. With current knowledge, it is perhaps advisable to recommend:

1. SABA & SAMA will continue to be necessary for the relief of intermittent symptoms and for use as rescue medication.
2. LABA and LAMA are suitable as maintenance (daily) treatment in patients with persistent symptoms.

Table 6: Selective Matrix Metalloproteinases (MMP) Inhibitors under study

Drug/ Molecule	Group	Action	Status
AZ11557272	Dual MMP9–MMP12 inhibitor	Prevent emphysema, small airway fibrosis, and inflammation in guinea pigs	Clinical development has recently been stopped
AZD1236	Orally Dual MMP9–MMP12 inhibitor	Failed biomarker endpoints, initial promising results	Further development aborted

Table 7: Humanized monoclonal antibodies targeted to alpha subunit of the interleukin (IL)-5 receptor (IL-5Rα)

Drug	Status	Action
Benralizumab	Phase III development	Reduce COPD exacerbations and improve symptoms in patient with higher blood eosinophils Improvement in lung functions, and disease-specific health status
Mepolizumab	Phase III development	Approved by the U.S. FDA in severe asthma EU in December 2015

3. After cost of therapy reduces to sensible level, Ultra-LAMA and Ultra-LABA appear tempting due to once daily convenience and lesser adverse reactions as claimed by their developers.
4. Patients with COPD Group D or with Asthma-COPD Overlap Syndrome may be ideal for triple-inhaler therapy (LABA+LAMA+ICS).
5. Frequent exacerbators COPD patients, those with lower respiratory tract bacterial colonization, or those with coexistent bronchiectasis may achieve beneficial efficacy with selective PDE4 inhibitor and/or long-term antibiotic prophylaxis.

FUTURE ANTICIPATIONS

Patients with uncontrolled disease despite taking both LAMA and LABA would likely be referred for specialist evaluation at a dedicated COPD centre in hopes to identify a specific COPD phenotype that might be suitable for specific and tailored targeted therapeutic pharmacotherapy. Of course, the objectives shall remain to reduce symptoms, to prevent and reduce the number of exacerbations, to prevent the rapid decline in lung function, to achieve reversal of corticosteroid insensitivity and to control the fibrotic progression while reducing the emphysematous process.

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