Drug Treatment of Stable COPD

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the common causes of morbidity and mortality in the world, and is increasing in prevalence. The pharmacologic treatment has evolved considerably during the past several decades. No current treatment prevents the relentless progression of airflow limitation that characterizes the disease. COPD is now considered to be both preventable and treatable. Current drug therapy for stable COPD focuses primarily on bronchodilation through inhaled β2-agonists and anticholinergic agents, which also reduce the hyperinflation of the lungs. Longer-acting bronchodilators are more convenient and may have additional advantages. The long-acting anticholinergic 'tiotropium' has shown to improve spirometric parameters, quality of life and utilization of health-care resources. Combinations of bronchodilators may offer additive effects and possibly, synergies. Inhaled glucocorticoids, although unable to alter the loss of forced expiratory volume in 1 second (FEV1) when used alone, may reduce exacerbation frequency and health status deterioration and improve mortality. Moreover, inhaled glucocorticoids may offer benefits in combination with long acting β2-agonists. There is a pressing need to develop new classes of therapy, and several new drugs are currently in development with the phosphodiesterase inhibitors in the advanced stages and being expected in the near future.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a severe respiratory condition that is increasing in prevalence worldwide. It is currently the fourth leading cause of death in the UK and US, and predicted to rank third in the global impact of disease by the year 2020.[1] According to a 1998-survey, non-communicable diseases (NCDs) are responsible for 32% of all deaths in India (approximately three million deaths per year). Of these chronic respiratory diseases constituted 6.7%.[2]

According to the latest ATS/ERS 2004 guidelines for the management of COPD, the condition has been defined as "A preventable and a treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences." [3]

Three conditions comprise COPD, namely mucus hypersecretion, emphysema (alveolar destruction) and bronchiolitis (small airways disease). The contribution of each component to airflow obstruction, pathophysiology and clinical symptoms varies between individual patients.

Cigarette smoking is a major risk factor for the development of COPD and accounts for more than 85% of the cases. However, only 10-20% of smokers develop COPD, which suggests an underlying genetic susceptibility. Other risk factors include air

Table 1 : Estimated morbidity and mortality due to NCDs in India

NCD (Year)	Morbidity		Mortality	
	Total no. of cases	Source of data	Total no. of deaths	Source of data
Cancer (1998)	593,803	Cancer registry	292,567	National HH survey and death certification
IHD (1998)	25 million	From ad hoc surveys	119,936	National HH surveys
Stroke (1998)	1 million	From ad hoc surveys	102,620	Rural HH survey and death certification
Diabetes (1998)	28 million	From ad hoc surveys	21,000	Based on hospital data
Chronic respiratory disease (1998)	65 million	From ad hoc surveys	577,837	Rural HH survey and death certification
Injuries (1998)	69 million	From ad hoc surveys	749,983	Rural HH Survey and death certification

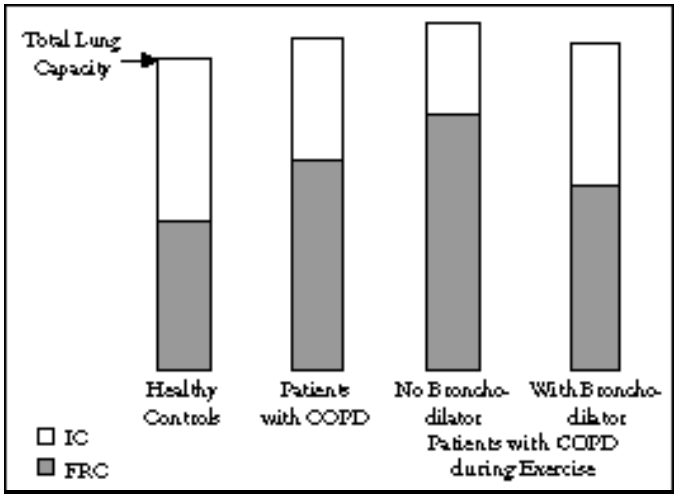

Fig. 1 : Pulmonary hyperinflation in patients with COPD and as compared with healthy controls, patients with COPD have pulmonary hyperinflation with an increase in functional residual capacity (FRC) and a decrease in inspiratory capacity (IC). Hyperinflation worsens with exercise and therefore reduces exercise tolerance (dynamic hyperinflation). Inhaled bronchodilators improve dynamic hyperinflation, as well as hyperinflation at rest (not shown) thereby reducing the work of breathing and increasing exercise tolerance.

pollution, chest infections in infancy, latent virus infections and low dietary intake of antioxidants.[1]

Despite the enormous advances in asthma management that have taken place over the last 10 years, there have been relatively few developments in the management of COPD. None of the existing drug therapies is able to slow the relentless progression of airway obstruction, so treatment is largely based on improving lung function with bronchodilators, together with changes in lifestyle. The management of COPD has now been formalized in guidelines produced in several countries. All of these guidelines propose escalating treatment, depending on the severity of airflow obstruction.

MANAGEMENT OF STABLE COPD

The major goals of therapy include smoking cessation, symptom relief, improvement in physiological function and limitation of complications, such as abnormal gas exchange and exacerbations of the disease. An integrated approach to the treatment combines healthcare maintenance and use of drug and supplemental therapies in a step-wise fashion as the disease progresses.[4]

Smoking cessation

Stopping smoking is the single most beneficial management strategy and the only intervention that reduces the accelerated decline in lung function and is important even in the elderly patients with severe disease. There are several ways to encourage smoking cessation. Psychological counseling, group therapy, and smoking reduction clinics may be useful for some patients. Nicotine replacement therapy doubles long-term (6-12 month) abstinence rates, and is available as chewing gum, skin patches, nasal sprays, and inhalers but these are not easily available in India. Bupropion is an effective smoking cessation aid in patients with COPD. It acts through stimulating noradrenergic activity, and is more effective than nicotine replacement therapies. Quit rates for persons taking bupropion who have smoked atleast one-half pack of cigarettes per day have doubled compared to those not taking the drug. Bupropion may be taken alone or in combination with nicotine replacement products.

Bronchodilators

Inhaled bronchodilators are the foundation of pharmacotherapy for COPD because of their capacity to alleviate symptoms, decrease exacerbations of disease and improve quality of life. These drugs also improve airflow limitation and hyperinflation, thereby decreasing the work of breathing and improving exercise tolerance. Paradoxically, improvement in function resulting from the administration of bronchodilators is not always reflected by changes in FEV_1 and FVC, and measurement of lung volumes or inspiratory capacity may be necessary to document physiological improvement [4] (Fig 1). In addition, bronchodilators may reduce respiratory muscle fatigue (controversial) and improve mucociliary clearance.[5] The choice of bronchodilators includes short and long-acting β_2-agonists, anticholinergics and theophylline.

Anticholinergics (Tiotropium, Ipratropium)

Normal airways have a small degree of vagal cholinergic tone, but because the airways are patent there is no perceptible effect and does not reduce airflow. However, when airways are irreversibly narrowed in COPD, vagal cholinergic tone has a much greater effect on airway resistance for geometric reasons. Since vagal cholinergic tone appears to be the only reversible element in the airflow obstruction of COPD, anticholinergics are the most effective class of bronchodilators in the treatment of COPD. They act by blocking the effects of acetylcholine, which is released from parasympathetic nerves in the airways, which contributes to bronchoconstriction in patients with COPD. In addition, anticholinergics may reduce mucus hypersecretion.[6]

Acetylcholine causes activation of muscarinic receptors at the level of the target cells such as bronchial smooth muscle and goblet cells. Muscarinic M_1 receptors are present in parasympathetic ganglia in the bronchial walls, and M_2 receptors are found pre-junctionally on post-ganglionic cholinergic nerves. The most important receptor for the effects of acetylcholine is however, the M_3 receptor, because M_3 receptor blockade will reduce all cholinergic bronchoconstrictor responses [6] (Fig 2).

Non-selective anticholinergics, such as atropine and ipratropium bromide, act on M_1, M_2 and M_3 receptors. Blockage of M_1 and M_3 receptors leads to bronchodilation. However, blocking prejunctional M_2-receptors leads to an increase in acetylcholine release and this may work against the post-junctional blockade of M_3-receptors, making these antagonists less efficient. [5] Like ipratropium bromide, tiotropium bromide is a quaternary ammonium derivative that binds to muscarinic receptors. However, although tiotropium binds with high affinity to muscarinic receptors of M_1, M_2 & M_3 subtypes, it dissociates very slowly from M_1 & M_3 receptors but more rapidly from M_2-receptors, thereby giving it a 'unique kinetic selectivity.' [6]

Tiotropium once-daily from a dry powder inhaler at 18 mcg has shown to cause greater improvement in lung function and reduction in symptoms than ipratropium bromide given four times daily[7] (Fig 3). Furthermore, clinical studies over a one-year period have demonstrated that tiotropium has impressive

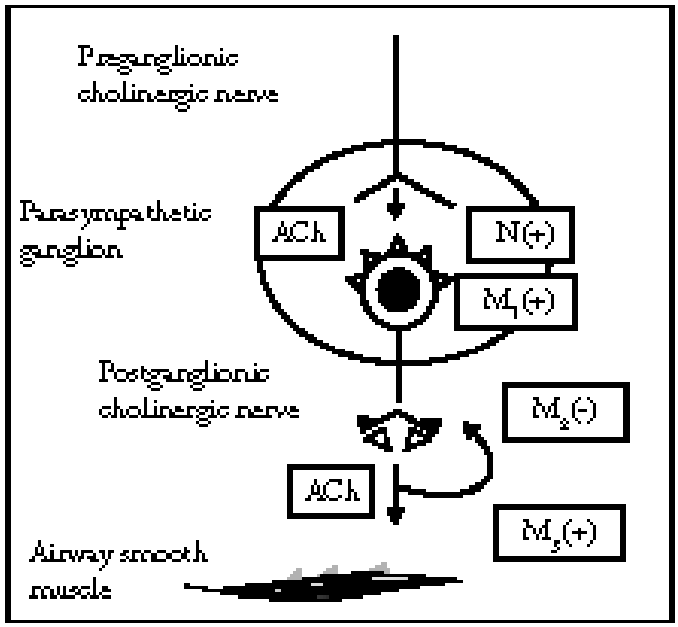

Fig. 2 : Muscarinic (M) receptor subtypes in the parasympathetic innervation of the airways. Ganglionic transmission is mediated by both nicotinic receptors (N) and M_1-receptors in a facilitatory role. M_2-receptor at thepostganglionic nerve terminal inhibit the release of acetyl choline (ACh), which acts on M_3- receptors to cause bronchoconstriction through contraction of airway smooth muscle.

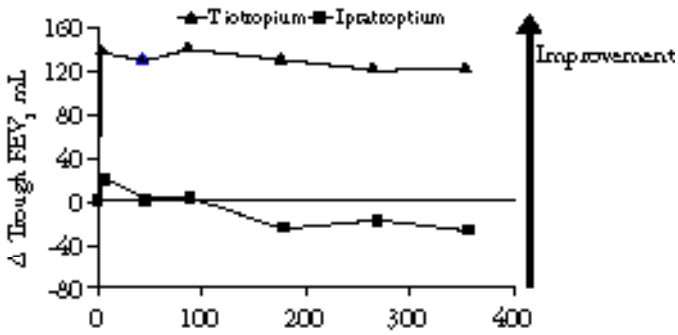

Fig. 3 : Mean change (Δ) in trough FEV1 following inhalation of tiotropium (▲) or ipratropium (■) at baseline (-) and throughout the 1 year trial ($p<0.001$) at all time points

and maintained effects on lung function, symptoms and health related quality of life (HRQoL) as measured by the St. George's Respiratory Questionaire (SGRQ), and may also reduce exacerbations. In a large scale comparative study over six months, tiotropium has shown superior bronchodilation and symptomatic improvement when compared to twice daily salmeterol in COPD.[8] Recently, tiotropium has also shown to reduce lung volumes thereby reducing dynamic hyperinflation. Reduced dynamic hyperinflation with a reduction in residual volume and functional residual capacity causes an increase in the inspiratory capacity[9] (Fig 4). This may contribute to symptomatic benefits, as this makes breathing more comfortable and dyspnea is lessened. Based on all these promising features, tiotropium has emerged as first-line maintenance treatment for patients with airway obstruction due to COPD.

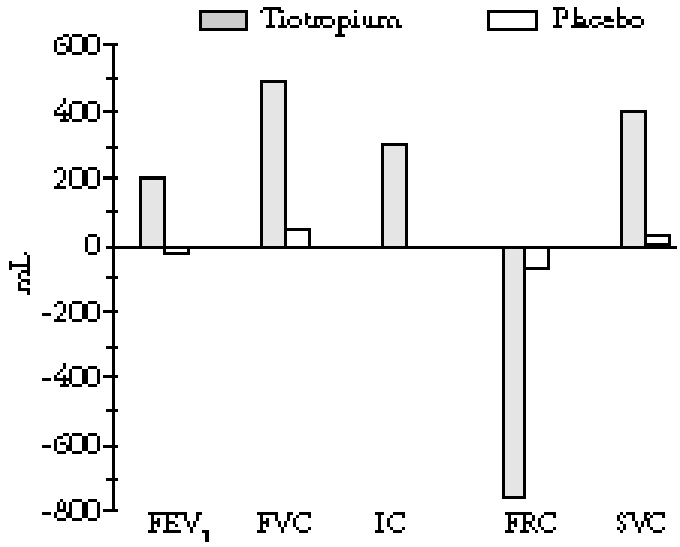

Fig. 4 : Changes in lung volumes and spirometry following 4 weeks of treatment with tiotropium or placebo

β_2-*agonists (Salbutamol, Salmeterol, Formoterol)*

β_2-agonists are bronchodilators that improve lung function, reduce symptoms and protect against exercise-induced dyspnea in patients with COPD. These agents induce bronchodilation by causing prolonged relaxation of airway smooth muscle. Smooth-muscle relaxation is due to β_2-adrenoceptor-mediated activation of adenyl cyclase in airway smooth muscle, which in turn increases the concentration of intracellular cAMP. Short acting inhaled β_2-agonists, such as salbutamol usually is given 'as required' for symptomatic relief. Salbutamol is also commonly used to test for bronchodilator reversibility. An increase in FEV_1 that is both greater than 200 ml and 12 % above the pre-bronchodilator FEV_1 is considered significant.

Several recent studies have demonstrated that the long-acting β_2-agonists salmeterol and formoterol are useful as maintenance therapy in COPD and give better symptom control than short-acting β_2-agonists. Long-acting bronchodilators are not appropriate for the treatment of acute symptoms. They have been shown to be effective in improving postbronchodilator FEV_1, exercise capacity and dyspnea scores in placebo-controlled studies.[10-12] However, in addition to prolonged bronchodilation, long acting β_2-agonists (LABA's) exert other effects that may be of clinical relevance. These include inhibition of airway smooth-muscle cell proliferation and inflammatory mediator release, as well as non-smooth-muscle effects, such as stimulation of mucociliary transport, cytoprotection of the respiratory mucosa and attenuation of neutrophil recruitment and activation[13] (Fig. 5).

Theophylline

Theophylline is still useful in the management of COPD, but it tends to be used as a third choice after anticholinergics and β_2-agonists. It has bronchodilator action and also improves symptoms by deflating the lungs, presumably via an action on the peripheral airways. Benefits have to be weighed against side effects, and monitoring of plasma levels may be necessary in elderly patients, as several factors can affect plasma concentrations. Cigarette

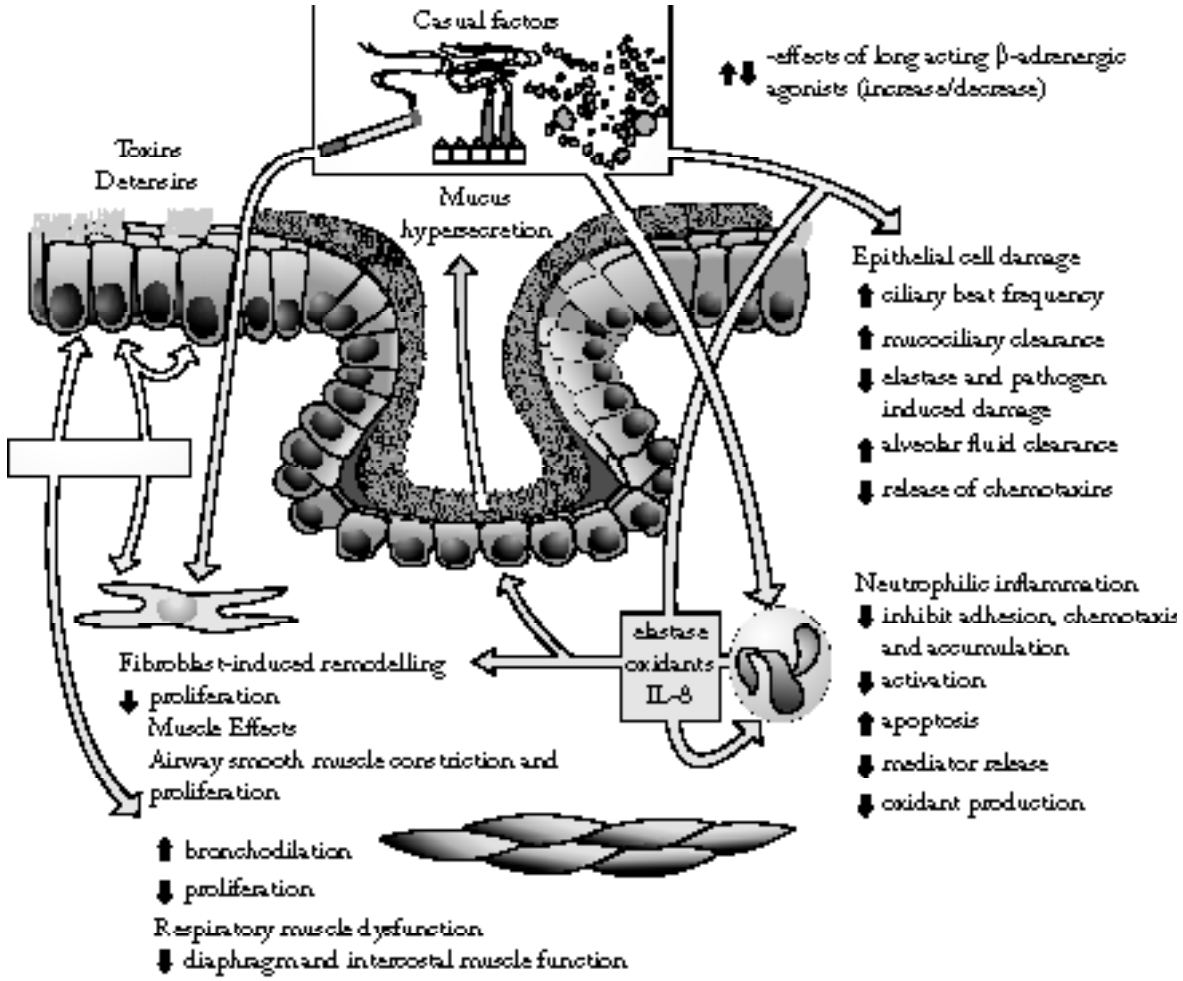

Fig. 5 : Long-acting β_2-adrenergic agonists in COPD. Scienific rationale. Potential mechanisms involved in the development of airflow limitation in COPD.

smoking increases metabolism, whereas old age itself, cardiac failure, liver disease, pneumonia and drugs that interfere with hepatic metabolism decrease clearance.[14] Theophylline may also have anti-inflammatory effects in patients with COPD. Unlike corticosteroids, low-dose theophylline recently has been found to reduce inflammatory markers in induced sputum and therefore, may be a useful treatment in the long-term management.[15] These anti-inflammatory effects occur at lower concentrations of theophylline (5-10 mg/L), and, therefore, there are fewer problems with side effects. There is a useful additive effect between theophylline and long-acting β_2-agonists in COPD.

Corticosteroids

The role of corticosteroids in the management of COPD remains controversial. Many studies have shown that inhaled corticosteroids (ICS) do not substantially modify airway inflammation in COPD and four large, long-term clinical trials comparing inhaled steroids with placebo found that these drugs do not appreciably alter the rate of decline in lung function. [16-19] However, some of these same trials have demonstrated that treatment with ICS alleviates patient's symptoms, reduces frequency of exacerbations and health status. The present knowledge supports the use of inhaled steroids in patients with moderate-severe COPD (FEV_1 < 50 %) with recurrent exacerbations.

It is important to recognize that in older patients the side effects of ICS are not well understood, and the use of these drugs should be carefully considered. Since it is difficult to predict accurately which patients will benefit from therapy, clinical and spirometric responses should be assessed in the months after the initiation of ICS. Treatment should be discontinued if no substantial clinical or physiological improvement is seen, since there is no evidence that continuing treatment with ICS provides any long-term benefit in such cases.

Combination Therapy for COPD

Combination bronchodilators

For patients who are not sufficiently controlled on monotherapy, GOLD guidelines and other current international guidelines for the management of COPD recommend combination therapy with two long-acting bronchodilators.

Combined use of inhaled long-acting β_2-agonists (LABAs) with tiotropium bromide should provide important therapeutic benefits, as these drugs have distinct and complementary pharmacological actions in the airways viz; different sites of

Table 2 : Effect of commonly used medications on important clinical outcomes in chronic obstructive pulmonary disease

	FEV_1	Lung volume	Dyspnoea	HRQol	AE	Exercise endurance	Disease modifier by FEV_1	Mortality	Side-effects
Short-acting β-agonists	Yes (A)	Yes (B)	Yes (A)	NA	NA	Yes (B)	NA	NA	Some
Ipratropiu, bromide	Yes (A)	Yes (B)	Yes (A)	No.(B)	Yes (B)	Yes (B)	No	NA	Some
Long-acting β-agonists	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	No	NA	Minimal
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	NA	NA	Minimal
Inhaled corticosteroids	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	NA	NA	Some
Theophyline	Yes (A)	Yes (B)	Yes (A)	Yes (B	NA	Yes (B)	NA	NA	Important

FEV_1 : Forced expiratory volume in one second; HRQoL : Health-related quality of life : AE exacerbation of COPD; NA : evidence not available GOLD grade levels are indicated in brackets.

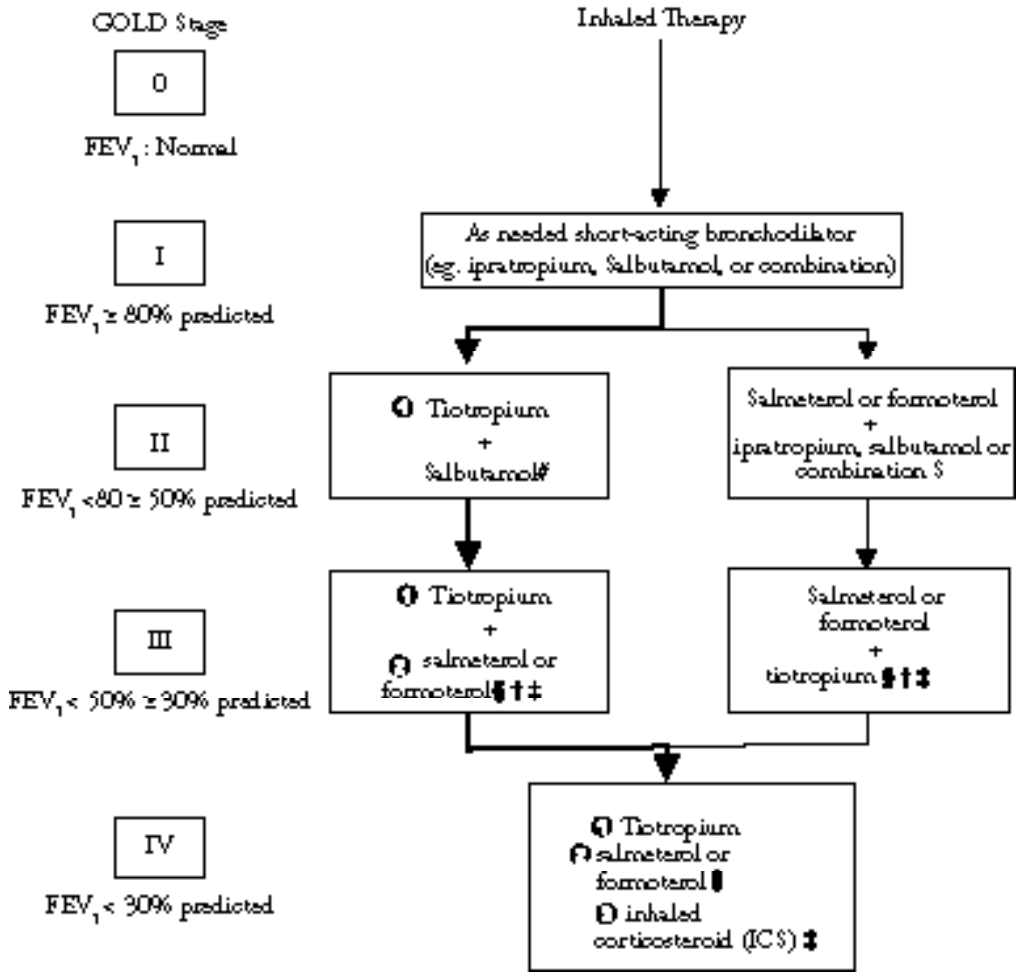

Fig. 6 : The proposed-three step algorithm for mild, moderate and severe COPD. (Left-hand pathwayis preferred) § short-acting bronchodilator as needed † ICS in frequent exacerbations or patients with a steroid respone ‡ Low-dose methylxanthines if inhaled bronchodilator response inadequate.

action, effects on mucus secretion, non-bronchodilator effects, leading to possible synergism.

Clinical experience with a combination of a short acting β_2-agonist (salbutamol) and anticholinergic (ipratropium bromide), in COPD is well established.

Preliminary data on the once-daily combination of Tiotropium (18 mcg) and Formoterol (12 mcg) have shown that the bronchodilation produced by the two agents given once daily together is of a greater magnitude than that of either component alone. Also combination therapy provided significant additive spirometric improvements even in COPD patients who failed to reach a pre-defined threshold response to salbutamol.[20,21]

Recently a double-blind, double-dummy, cross-over, randomized, pilot study was published which compared the acute bronchodilator efficacy of single doses of formoterol, tiotropium and the combination of tiotropium with formoterol in patients with stable COPD. [22] The combination resulted in rapid onset

of action (due to formoterol), a higher peak effect (vs either each agent alone) and sustained bronchodilation.

ICS and LABA combinations

Combining a long-acting β_2-agonist and an ICS as maintenance therapy has been very successful in managing bronchial asthma. There is an increasing body of evidence showing that such a combination can provide an effective treatment option for COPD patients as well.

This type of therapy not only improves airflow obstruction but also provides clinical benefits, as manifested by sustained reduction in overall symptoms, improvements in HRQoL and reductions in exacerbations.[23,24] The TRISTAN (trial of inhaled steroids and long-acting β_2-agonists) study showed that combination of salmeterol/fluticasone resulted in statistically significant improvement in number of exacerbations, FEV_1, quality of life and respiratory symptoms.[23]

Other Medications

'Thinning' of viscous airway mucus with mucolytic drugs is one way of improving clearance, both by cough and by mucociliary transport. However, although numerous mucolytic drugs are available worldwide, their effectiveness in treatment of stable COPD has not been established. Consequently, they are not generally recommended in current guidelines on management. However, two rigorous meta-analyses demonstrate that treatment for at least two months with mucolytic drugs, especially N-acetylcysteine, reduces exacerbations and days of illness.[25,26] However, it is uncertain whether the beneficial effects of N-acetylcysteine (or the other drugs) are due to its mucolytic or antioxidant properties (or both).

APPROACH TO PHARMACOTHERAPY OF COPD

Table 2 shows the effects of different drugs on various outcomes in COPD.[3] Based on the role of LABAs in the management of stable COPD, Tashkin and Copper have recently proposed a three step algorithm for mild, moderate and severe COPD which could support physicians in their therapeutic choice[27] (Fig 6). In stable disease, administration by means of a metered-dose or dry-powder inhaler is preferred.

FUTURE THERAPIES

There is a pressing need to develop new therapies, as existing treatments do not alter the progressive course of the disease. There have been relatively few advances in the therapeutic options for the treatment of COPD, but better understanding of the molecular mechanisms involved in the pathogenesis of COPD will undoubtedly lead to improved therapies in the future. The ultimate aim is to identify treatment strategies that slow or stop disease progression.

Data from one-year studies have suggested that tiotropium may reduce the rate of decline in FEV_1 overtime compared to placebo. In this regard, results of the 4-year "Understanding Potential Long-term Impacts on Functions with Tiotropium" (UPLIFT) trial are awaited with interest. The UPLIFT trial has been initiated to evaluate the potential long-term impact of tiotropium on lung function decline and disease progression in patients with COPD. If it is shown that tiotropium could reduce the rate of decline in lung function, this would be a major breakthrough in COPD treatment. Another study the "TOwards a Revolution in COPD Health" (TORCH) survival study is aiming to determine the impact of salmeterol/fluticasone propionate combination and the individual components on the survival of COPD patients.

Of the emerging therapies for the treatment of COPD, agents in the phosphodiesterase-4 (PDE-4) inhibitor class are the most extensively studied. They are enzymes that inhibit the release of cytokines and chemokines through the increase of 3′,5′-cAMP. These are the primary enzymes found in the cells of inflammation. Roflumilast is the most potent and promising of all the available PDE-4 inhibitors and is currently undergoing phase III trials.

CLINICAL HIGHLIGHTS

- Currently, bronchodilators are the treatment of choice for symptoms of COPD because they counter the central and only known reversible pathophysiologic defect: increased tone of airway smooth muscle.
- Bronchodilator combinations, such as salbutamol/ipratropium, salmeterol/ipratropium, and theophylline/ipratropium, have been effective in patients with COPD, and their pharmacologic effects are complementary in patients with obstructed breathing.
- If dyspnoea remains after a patient has been treated maximally with bronchodilators, a trial with inhaled corticosteroids is reasonable.
- Inhaled corticosteroids can help prevent exacerbations, particularly in patients with severe pulmonary function abnormalities who are at increased risk. Systemic corticosteroids are recommended only for treatment of acute exacerbations.
- Novel short and long-acting bronchodilators are being investigated. In the future, selective phosphodiesterase-4 inhibitors may combine bronchodilatory and anti-inflammatory activity.

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