Pharmacological therapy of chronic obstructive pulmonary disease

COPD is a highly preventable and treatable disease, the latter often being forgotten.

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Chronic obstructive pulmonary disease (COPD) is a multi-component disease that is highly preventable and treatable.[1] The predominant presenting feature is one of progressive dyspnoea. This occurs as a result of airflow limitation due to a combination of damage to the airways and parenchyma.[1] The other important aspects of the disease are the presence of an abnormal inflammatory response and the presence of systemic manifestations.[1] Treatment of COPD is effective in multiple patient-centred outcomes,[2] and this has been demonstrated in a number of treatment studies over the last decade.

All symptomatic patients with COPD require pharmacological therapy.

Current literature suggests that smoking cessation, long-term oxygen therapy in hypoxaemic patients, non-invasive ventilation, and lung volume reduction surgery in selected patients improve survival.[1,2] The recent TORCH study[3] of more than 6 000 patients showed that the combination of salmeterol and fluticasone not only improved lung function and health status, but also reduced the relative mortality risk by 17.5% over the 3 years of the study in comparison with placebo. Other therapies improve symptoms and lung function as well as quality of life.[1] All symptomatic patients with COPD require pharmacological therapy. This should be determined by the severity of symptoms and the degree of pulmonary dysfunction. Clearly the patient's tolerance to the various drugs will influence the choice of long-term maintenance treatment. The other important factor in the developing world is affordability and access to the pharmacological agents.

This article will summarise the current knowledge with respect to pharmacological therapy of COPD. The goals of the treatment of COPD are to prevent further deterioration in lung function, improve symptoms and quality of life, prevent and treat complications, and prolong a meaningful life.[1,2]

Bronchodilators

Bronchodilators are used as first-line agents for the symptomatic treatment of patients with COPD.[1,4] Bronchodilators decrease airway smooth-muscle tone, thus improving lung emptying during expiration and hence decreasing lung hyperinflation.[5] This reduces dyspnoea both at rest and on exertion, with resultant improvement in effort tolerance.

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Short-acting anticholinergics and beta$_2$-agonists have been shown to improve pulmonary function, dyspnoea, and exercise performance in patients with COPD.[1,5] Individual responses to different agents may vary. Combining short-acting beta$_2$-agonists and anticholinergics produces superior bronchodilation than either agent alone.[5]

In patients with persistent symptoms it is preferable to use long-acting bronchodilators.[1,2,5] Long-acting beta$_2$-agonists (LABAs) improve symptoms, increase exercise endurance and improve quality of life.[2] The recent TORCH study[3] has been reassuring with respect to the safety profile of salmeterol in COPD.

Treatment with tiotropium, a long-acting anticholinergic, has been associated with improvements in lung function, quality of life and exacerbations in a recently completed 4-year study in patients with COPD.[6] This study (UPLIFT) was reassuring about the safety of the drug with long-term use in patients with COPD.

Theophylline is a nonspecific phosphodiesterase inhibitor and has bronchodilator effects at higher doses, where there is a higher risk of toxicity. It is recommended for patients who have difficulty using inhaler devices. The previously recommended therapeutic serum levels of 15 - 20 mg/dl are too close to the toxic level and a lower level of 8 - 13 mg/dl is therefore suggested as safer but still effective.[2] Specific phosphodiesterase E4 inhibitors such as cilomilast and roflumilast are currently undergoing clinical trials. They may have anti-inflammatory and bronchodilator properties but preliminary results show a modest bronchodilator effect and some benefits on quality of life.

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COPD is a progressive disease, and a stepwise increase in treatment is recommended in most guidelines.[1,4,5] Combination therapy produces better bronchodilation than individual agents.[7] It is recommended that one commences treatment with inhaled short-acting bronchodilators either alone or in combination; if that treatment is not successful, one could change to one of the long-acting bronchodilators. Combining bronchodilators from different pharmacological classes has been proven to be effective in patients with COPD.[7] Individual patients may vary in their response to the various agents. As the disease progresses, it is often necessary to use two or more bronchodilator agents from different classes to obtain symptomatic relief.

Corticosteroids

Inhaled corticosteroids (ICS) as monotherapy

The anti-inflammatory effects of corticosteroids in COPD are modest in comparison to asthma.[2] Several studies have looked at the effect of ICS in slowing down the progressive decline in lung function in COPD. The results have been disappointing. There was minimal, if any, benefit in the rate of decline in lung function. However, there has been evidence of a reduction in exacerbation frequency and improvement in quality of life.[2,5] In the TORCH study[3] ICS (fluticasone) did not show clinically significant effects on mortality compared with placebo, and although there were statistically significant improvements in health status, pulmonary function and exacerbation frequency, the clinical significance of these findings remains debatable. The combination of LABAs and ICS was superior in all endpoints studied compared with ICS alone. It is therefore suggested that in patients with COPD, ICS should not be used alone but rather in combination with a LABA.

ICS/LABA combination

The TORCH study showed the benefits of the combination of ICS/LABA on FEV_1, exacerbation rate, quality of life and survival compared with placebo and either of the monocomponents.[3] There was an increased incidence of pneumonia (not confirmed on chest radiography or sputum culture) in patients receiving ICS but this was not associated with an increase in mortality. The Optimal Therapy study[8] compared the addition of placebo, salmeterol or the combination of salmeterol/fluticasone with tiotropium. Although exacerbation rate, the primary outcome, was similar in the three groups, lung function, health-related quality of life and hospitalisations were better in the group receiving tiotropium and salmeterol/fluticasone. In contrast to the TORCH study, no increased incidence of pneumonia was observed for the corticosteroid arm. There is an additive benefit for ICS and LABAs in COPD and this is an additional reason for using the ICS/LABA combination rather than ICS alone.

Systemic corticosteroids

In stable COPD there is no role for chronic use of systemic corticosteroids. No study so far has shown any benefit of chronic systemic use of these agents in patients with stable disease. Long-term use of systemic corticosteroids is definitely associated with toxic effects such as hyperglycaemia, myopathy, hypertension and osteoporosis, all of which are more pronounced in the elderly.[9]

Summary and recommended treatment

Treatment of patients with COPD is dictated by the severity of lung function impairment, symptoms and deterioration of effort tolerance. Therefore, unlike in asthma, as the disease progresses the treatment requires a progressive increase in the number of pharmaceutical agents, often used in combination to achieve the desired effect of symptom relief. Fig.1 summarises the treatment approach.

Future pharmaceutical agents

There are a number of new drugs in development and some of them are listed below:

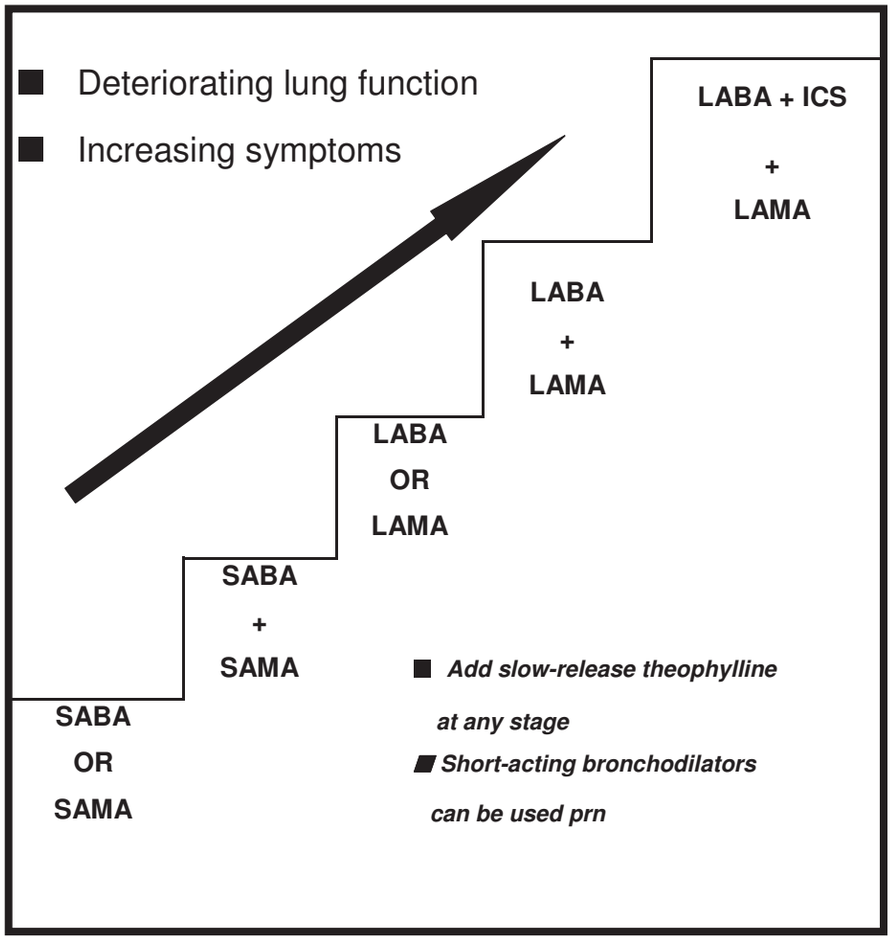

Fig.1. Pharmacological management of COPD. SABA = short-acting beta$_2$-agonist; SAMA = short-acting muscarinic antagonist; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

- inhaled long-acting bronchodilators, e.g. arformoterol (for nebuliser use), and carmoterol, indacaterol, and new long-acting anticholinergics[10]
- ICS/LABA combinations in once-daily formulations[10]
- antioxidant drugs such as N-acetylcysteine[10]
- retinoids which have been shown to possibly reverse the changes of emphysema.[10]

Conclusion

COPD is a preventable disease, and to those patients who have already developed the disease one can offer treatment tailored to their individual needs. The treatment will include both pharmaceutical agents as covered in this brief overview, and non-pharmaceutical interventions covered elsewhere.

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In a nutshell

- Chronic obstructive pulmonary disease is characterised by progressive dyspnoea, cough and sputum production.
- Pharmacological therapy is aimed at alleviating symptoms, improving effort tolerance, reducing exacerbations and prolonging a meaningful life.
- The main therapeutic agents used are bronchodilators (short- and long-acting), inhaled corticosteroids, theophyllines and various combinations of these products.
- A number of newer agents are currently in various phases of development.

Single Suture

Damping vaginal inflammation may help prevent HIV

Preventing vaginal inflammation may prevent women from becoming infected with HIV, if studies on female macaques can be extrapolated to humans. Ashley Haase and colleagues from the University of Minnesota have found that a few epithelial cells on the cervix of femal macaques are the first point of entry for simian immunodeficiency virus (SIV). Nearby immune cells respond by emitting molecules that trigger inflammation and summon T-cells to the cervix. These would normally destroy invaders, but T-cells are the cells that SIV (and HIV) use to infect their host.

Studies of toxic shock syndrome have already identified chemicals that can suppress vaginal inflammation, including glycerol monolaurate, a constituent of vegetable oils. When Haase's team mixed glycerol monolaurate with vaginal lubricant and applied it to the vaginas of 5 macaques, they found that the animals resisted infection, even after repeated exposure to SIV. The chemical appeared to block the immune reaction that summons the T-cells to the cervix.

It is not yet clear whether glycerol monolaurate would block HIV in a woman's cervix already inflamed by other infections, or whether blocking cervical immune responses might leave her less protected against other infections. However, the team argues that even if the gel – which costs less than $0.1 per dose is – only 60% effective, it would prevent nearly a million infections a year and might slow the heterosexual transmission of HIV in Africa.

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