



Where current pharmacological therapies fall short in COPD: symptom control is not enough

N. Roche

ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a common and progressive condition that is currently the fourth leading cause of death worldwide. There is now a large body of evidence indicating that both pulmonary and systemic inflammation are present in patients with stable COPD and may underlie both respiratory symptoms and common comorbidities of this disease. Smoking cessation and long-term oxygen therapy have been shown to change the course of COPD and recent results obtained with the combination of fluticasone and salmeterol have indicated that it could decrease mortality and slow the decline in lung function in patients with this disease. However, some pharmacological treatments can significantly improve dyspnoea, exercise tolerance, limitations in activity, rate of exacerbations and quality of life (e.g. long-acting bronchodilators and inhaled corticosteroids combined with a long-acting β_2 -agonist). The ability of these agents to modify the rate of disease progression remains to be firmly established in large-scale, long-term trials.

The concept of disease modification itself in COPD may need to be revisited and more precisely defined in terms of markers and clinical outcomes, including extrapulmonary manifestations: agents that durably affect symptoms, activities, exacerbations and quality of life should probably be considered as disease modifiers. It is also reasonable to suggest that early diagnosis and treatment of patients with COPD might be the first and potentially most important disease-modifying intervention.

There is clearly a need for new therapies that directly target the specific inflammatory processes underlying chronic obstructive pulmonary disease and its pulmonary and extrapulmonary manifestations.

KEYWORDS: β_2 -agonists, chronic obstructive pulmonary disease, disease progression, inflammation, inhaled corticosteroid

Chronic obstructive pulmonary disease (COPD) is a common, heterogeneous and progressive condition with airflow limitation that is not fully reversible and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, most notably those arising from cigarette smoke [1]. COPD is a major public health problem. It is currently the fourth leading cause of death in the world, and both the prevalence and mortality associated with COPD are expected to rise in coming decades [1]. COPD is the most rapidly rising cause of death in individuals >65 yrs of age, the fastest growing segment of the population in developed countries [2]. Disability from COPD is expected to rise through to 2020 with aging of the population and the associated increase in the prevalence of

chronic diseases. By that time, it will be the third most common cause of death [3].

Patients with COPD present with a variety of clinical findings, including respiratory and non-respiratory manifestations. The most characteristic respiratory symptoms include abnormal shortness of breath, chronic cough and excessive sputum production [1]. The latter two symptoms precede airflow limitation in many COPD patients [1] but they do not independently predict its occurrence, once tobacco smoking is taken into account [4]. Patients with COPD may also present with so-called "systemic" symptoms that may result from the chronic inflammatory nature of the disease [5]. Extrapulmonary manifestations that have been associated with COPD include systemic inflammation, nutritional

CORRESPONDENCE

N. Roche
Respiratory and Intensive Care
Medicine
Hôtel-Dieu
1 place du Parvis de Notre Dame
75004 Paris
France
Fax: 33 142348448
E-mail: nicolas.roche@htd.aphp.fr

STATEMENT OF INTEREST

N. Roche has received fees for speaking or consulting, funds for attendance at congresses, and fees for organising education or research from GlaxoSmithKline, Boehringer Ingelheim, Pfizer, Altana, Chiesi, Novartis and AstraZeneca.

depletion and weight loss, skeletal muscle dysfunction, cardiovascular disease, osteoporosis, anaemia and depression [5–7]. The relationship between COPD and cardiovascular disease may be particularly important since, in some studies, >50% of patients with COPD die from cardiovascular-related disease [5]. The pulmonary and extrapulmonary effects of COPD result in a wide range of deleterious effects on clinical outcomes, including decreased exercise tolerance, impairment to the ability to carry out daily activities, reduced life expectancy and decreased quality of life [1, 8].

The present article considers the possibility of a central mechanism, *i.e.* inflammation, underlying both the pulmonary and extrapulmonary symptoms of COPD. Such a mechanism would be a relevant target for treatments aimed at altering disease progression. The present article also discusses how disease modification should be defined and how current and future pharmacological treatments could achieve this goal.

INFLAMMATION AS A UNIFYING CONCEPT IN COPD

There is now a large body of evidence indicating that both pulmonary and systemic inflammation are present in patients with stable COPD [5]. The article by RENNARD [9] in the present issue of the *European Respiratory Review (ERR)* extensively describes the characteristics of airway inflammation, repair and remodelling in patients with COPD. For instance, several inflammatory markers have been shown to be elevated in the lungs or airways of smokers and patients with COPD, including interleukin (IL)-6, IL-8, IL-1 β , macrophage chemoattractant protein (MCP)-1, transforming growth factor- β and matrix metalloproteinase (MMP)-9 [10, 11].

A systematic review of results from studies available in 2004 also indicated that patients with chronic airflow limitation had significantly elevated levels of circulating C-reactive protein, fibrinogen, leukocytes and tumour necrosis factor (TNF)- α . This was true for both current and ex-smokers [5].

Systemic inflammation is also thought to play a key role in many comorbid conditions associated with COPD. This observation has prompted the suggestion of an individual predisposition to develop abnormal systemic inflammation in response to environmental aggressions (mainly tobacco smoke), where this response represents a common disease process in both COPD and its related comorbid conditions (fig. 1). Inhaled corticosteroids are the only currently available anti-inflammatory agents that have some efficacy on clinical outcomes in COPD (discussed further later) [12]. However, the magnitude of observed benefits is relatively limited, which may relate to some degree of molecular resistance to their effects on transcription, as a consequence of oxidative stress. These considerations suggest the need for new therapies that specifically target the inflammatory processes that characterise COPD, and for monitoring their effects on both the lungs and other organ systems [13].

Despite the generally accepted importance of inflammation in COPD [14], it is noteworthy that, to date, no strictly anti-inflammatory therapy evaluated has been definitely demonstrated to alter the natural course of the disease. Animal studies have indicated that airway remodelling can occur in the absence of inflammation, so it is possible that inflammation may be a consequence rather than a cause of COPD.

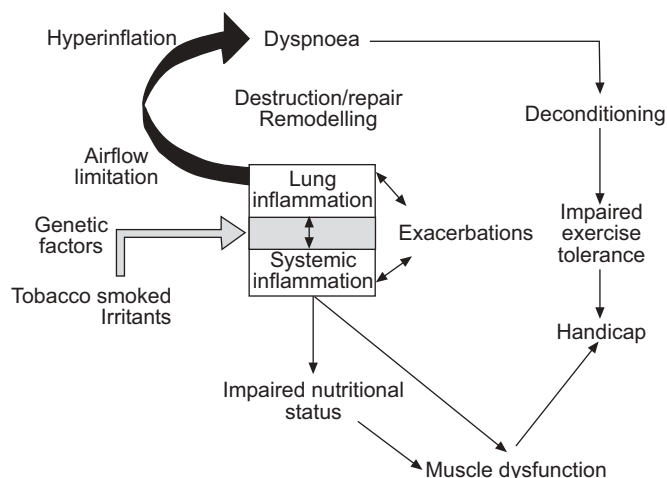


FIGURE 1. Inflammation as a unifying factor in the respiratory and systematic manifestations of chronic obstructive pulmonary disease (COPD). A combination of genetic and environmental (e.g. tobacco smoke) factors lead to airflow limitation, hyperinflation, lung destruction and remodelling, which result in COPD symptoms (dyspnoea). This leads to deconditioning, reduced exercise tolerance and handicap. Impaired nutritional status and inflammation contribute to muscle dysfunction. The occurrence of exacerbations amplifies and accelerates all of these processes. Data from [12].

OVERVIEW OF CURRENT TREATMENT FOR COPD

None of the existing treatments of COPD has been consistently shown to modify the course of the disease, as assessed by lung function decline and mortality. Thus, the remaining aims of current therapy are to decrease symptoms and exercise intolerance, improve activity and health status and reduce the risk for disease complications (e.g. acute exacerbations and chronic respiratory failure leading to cor pulmonale) [1]. Current therapeutic approaches for COPD include as-needed or regular bronchodilator medications (mainly inhaled anticholinergic agents, β_2 -agonists, and combinations of these agents) to reduce or prevent symptoms [1], inhaled corticosteroids (ICS) combined with long-acting β_2 -agonists, pulmonary rehabilitation, long-term oxygen therapy (LTOT) and, in highly selected patients, surgery [1].

Inhaled bronchodilators are central to the symptomatic treatment of patients with COPD and their use has been shown to decrease airflow limitation and static and dynamic hyperinflation, leading to lessened respiratory constraints and work of breathing. In this way, COPD-related dyspnoea and functional impairment are reduced, while exercise tolerance and patient activity increase. Bronchodilators also reduce the risk for acute exacerbations. In combination, these effects lead to improvements in quality of life [1, 15].

The purpose of using ICS in COPD is to decrease the severity of COPD symptoms and the frequency of exacerbations, and to improve health status [16]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends that ICS treatment should be used in addition to bronchodilators in patients with severe or very severe COPD (forced expiratory volume in one second (FEV₁) <50% predicted) who have repeated exacerbations [1]. However, practice surveys found that in COPD, ICS are frequently prescribed in situations that

do not fit this indication [17]. Finally, long-term treatment with oral glucocorticosteroids is not recommended for the treatment of patients with COPD: no obvious beneficial effect has been described with these agents, which can have many deleterious consequences, including impairments in bone density, nutritional status and peripheral muscle function, aggravation of comorbid diseases, lessening of the efficacy of pulmonary rehabilitation and even decreased survival [1, 18].

DISEASE-MODIFYING THERAPY IN COPD: THE CONSERVATIVE VIEW

A "conservative" view is that, to be considered as a "disease modifier", a treatment should decrease either the rate of lung function decline or mortality. Such effects are widely accepted for a few measures only, namely smoking cessation, LTOT and, most recently, the combination of ICS and a long-acting β_2 -agonist.

Smoking cessation

It is well established that smoking cessation can alter the course of disease in patients with COPD. The Lung Health Study (LHS) was a randomised clinical trial of smoking cessation and regular administration of an inhaled bronchodilator (ipratropium bromide) in 5,887 middle-aged smokers (35–60 yrs old at study entry) who had airway obstruction but no other serious illness. In the LHS, smoking cessation significantly decreased the rate of lung function decline [19]. Further follow-up of these patients 11 yrs after the start of the study showed that 38% of continuing smokers but only 10% of sustained quitters had an FEV₁ <60% pred [20]. Assessment of mortality at 14.5 yrs of follow-up indicated that smoking cessation decreased the risk of dying from the two leading causes of mortality, *i.e.* cancer and coronary heart disease (fig. 2) [21].

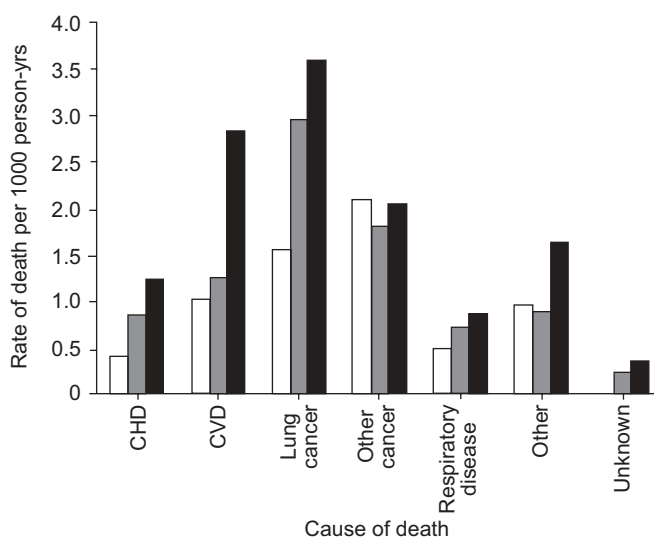


FIGURE 2. Mortality rates by cause at 14.5 yrs in the Lung Health Study. Only a small percentage of patients with chronic obstructive pulmonary disease die as a result of respiratory disease. Lung cancer and the combination of coronary heart disease (CHD) and cardiovascular disease (CVD) are the most common causes of death in these patients. □: sustained quitter; ■: intermittent quitter; ■: continuing smoker. Data from [21].

Long-term oxygen therapy

LTOT has the potential to affect the course of COPD in the most severe patients with chronic respiratory failure. Results from studies carried out by the Medical Research Council and the National Institute of Health over 25 yrs ago indicated that oxygen therapy administered for ≥ 15 h per day significantly improved survival in patients with marked COPD-related hypoxaemia [22, 23]. In contrast, other studies in patients with higher levels of arterial oxygen tension (7.3–8.7 kPa (55–65 mmHg)) have demonstrated no significant benefit of LTOT, even in subjects with nocturnal desaturation [24, 25]. Thus, LTOT improves survival only in the small minority of patients with the most pronounced hypoxaemia.

Bronchodilators

The long-acting anticholinergic agent tiotropium (one dose = 18 $\mu\text{g}\cdot\text{day}^{-1}$) has been demonstrated to improve lung function in a combined analysis of two identical placebo-controlled trials that included a total of 921 patients with stable COPD (mean age 65.2 yrs). The primary spirometric outcome was trough FEV₁, *i.e.* FEV₁ measured 23 h after the last treatment dose. Treatment for 1 yr resulted in an $\sim 12\%$ increase over baseline in trough FEV₁ and a 22% increase in mean FEV₁. Further analysis of results from these studies showed that the mean decline in trough FEV₁ between days 8 and 344 was 58 mL $\cdot\text{yr}^{-1}$ in the placebo group *versus* only 12 mL $\cdot\text{yr}^{-1}$ in the tiotropium group (fig. 3) [26]. The results of this analysis support the view that tiotropium has the potential to reduce the rate of decline in FEV₁ in patients with COPD and thus modify the course of this disease. However, longer-term trials specifically designed to study this effect are required to confirm this observation. Such an evaluation is currently being carried out in the

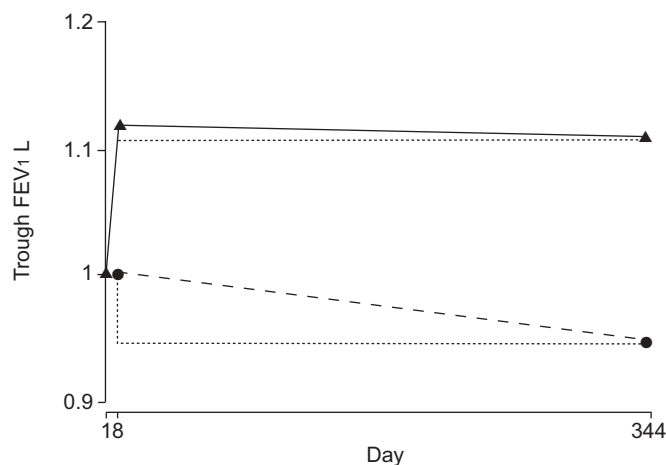


FIGURE 3. Mean change in trough forced expiratory volume in one second (FEV₁) (mL $\cdot\text{yr}^{-1}$) in tiotropium-treated (—; n=518) and placebo-treated (- - -; n=328) patients from 8 to 344 days after the beginning of treatment. The results are from a *post hoc* analysis of data from 921 ambulatory COPD patients participating in two 1-yr, double-blind tiotropium *versus* placebo-controlled trials. Serial spirometry was obtained at baseline (before the first dose of study drug), on day 8, at 6 weeks and at 3, 6, 9 and 12 months after the start of the study. The mean decline in trough FEV₁ between days 8 and 344 was 58 mL $\cdot\text{yr}^{-1}$ in the placebo group and 12 mL $\cdot\text{yr}^{-1}$ in the tiotropium group ($p=0.005$ *versus* placebo (mean regression slopes)). Reproduced and modified from [26] with permission from the publisher.

Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study, a large multicentre 4-yr trial, which is investigating the effects of tiotropium on lung function in up to 6,000 patients with COPD. The first results should be available in 2008.

Inhaled glucocorticoids combined with long-acting β_2 -agonists

Some studies suggested that ICS, either alone or combined with long-acting β_2 -agonists, could have an effect on mortality in COPD patients [27]. However, the studies suffered from methodological caveats: one was a meta-analysis of heterogeneous and individually negative trials [28], and the other was an observational study [29]. The 3-yr TOWARDS a Revolution in COPD Health (TORCH) study was designed to determine the impact of *b.i.d.* administration of the combination of salmeterol (50 μ g) and fluticasone propionate (500 μ g) on mortality in patients with COPD and a FEV₁ of <60% pred [30]. The study enrolled 8,554 patients and 6,184 were randomised to treatment with placebo, salmeterol, fluticasone or fluticasone plus salmeterol. The mean patient age at baseline was 65 yrs and FEV₁ was 44% pred for all groups. Combination treatment with fluticasone propionate and salmeterol resulted in a 17.5% reduction in mortality *versus* placebo that approached statistical significance ($p=0.052$). Noticeably, no such effect was observed with fluticasone propionate alone. Results from this study also indicated no increased risk for fractures in patients treated with fluticasone propionate alone or fluticasone plus salmeterol *versus* those who received placebo. Additional results from a subset of 658 subjects in the TORCH study indicated that ~20% in each group showed evidence of osteoporosis in hip and lumbar spine scans and another 40% had osteopaenia. At the end of 3 yrs, there was no statistical difference among the trial groups in terms of bone density loss. Patients in the placebo group lost a median of 3.1% density in their hip compared with 1.7% in the salmeterol group, 2.9% in the fluticasone group and 3.2% in the combination treatment group. Results for lumbar spine density indicated no change in the placebo group, a gain of 1.5% in the salmeterol group, and 0.3% losses in the fluticasone and combination treatment groups [31]. These results support the conclusion that long-term treatment with ICS does not increase the risk for osteoporosis in patients with COPD.

A selection of results therefore suggest that some available pharmacological treatments of COPD may fulfil the conditions required to be considered as disease modifiers, according to the conservative view mentioned previously. However, more data are awaited before a firm conclusion can be drawn. In parallel, it seems important to focus on several clinical outcomes, including exacerbations, daily activities and quality of life, which may reflect the effects of treatments on other aspects of the natural history of the disease.

DISEASE-MODIFYING THERAPY IN COPD: WIDENING THE PERSPECTIVE

The previously mentioned conservative definition of disease modification in patients with COPD could be too narrow, since survival and FEV₁ may remain unchanged despite relevant and durable improvements in clinically important outcomes, such as symptoms, time to LTOT, overall decline in health

status, exacerbations (frequency, duration and severity), and the course of COPD-associated systemic manifestations. Thus, focusing on lung function and mortality may ignore critical factors in the overall health of patients with COPD; assessing the benefit of therapy also requires accurate assessment of the effects on dyspnoea, fatigue, activities of daily living, work productivity, exacerbations and quality of life [32]. This is emphasised by the observation that, in patients with COPD, health status relates much more closely to physical function than to FEV₁; in addition, the systemic manifestations associated with COPD may be more important determinants of disability and overall health than pulmonary function in many individuals [33]. Finally, lung function may not be the most appropriate end-point to assess the anti-inflammatory effects of treatment that may be key to slowing or stopping disease progression.

Major issues when assessing the disease-modifying potential of a treatment are the required length of follow-up and number of patients, given the slowly progressive nature of the disease. Attempts to use "acute" response to treatments to predict patients' long-term effects have been unsuccessful [34]. In addition, corresponding measurements were dominated by FEV₁, which is a robust measure but correlates poorly with clinical outcomes [35]. Other lung function variables reflecting hyperinflation or avoiding dynamic airways expiratory compression have been proposed. However, although they do indeed correlate better than FEV₁ with, for example, dyspnoea, the correlation is not sufficiently strong to be used at the individual level [36, 37].

Therefore, biological (or possibly radiological) markers related to disease progression may be useful for the assessment of potentially disease-modifying therapies in patients with COPD. Useful biomarkers must be sensitive to therapeutic interventions, predictive of clinical outcomes and, if possible, responsive relatively quickly. At present, no such marker is available but several candidates are being studied, including markers of inflammation, protease-antiprotease balance and oxidative stress [38]. It is also crucial that candidate markers can be collected noninvasively, which explains the growing interest in exhaled gases and breath condensates or induced sputum. However, given the complexity of COPD pathophysiology, demonstrating biological effects on one or even several markers does not mean that a treatment will be clinically effective. Therefore, formal validation of the predictive potential of biomarkers is needed, which requires long-term clinical studies. Before such studies are completed, biomarkers can only be used for screening, which is already an important step in the development of new products.

EFFECT OF CURRENT PHARMACOLOGICAL TREATMENTS ON CLINICALLY IMPORTANT OUTCOMES IN COPD

Results from recent studies have suggested that several treatments may have the potential to alter some clinical aspects of the natural history of COPD. In the placebo-controlled trials mentioned previously, tiotropium was shown to reduce exacerbation rate and dyspnoea, thereby improving quality of life [39]. As described later, similar results were found with long-acting β_2 -agonists, ICS and their combination.

The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial was carried out to assess the effect of long-term ICS (500 µg *b.i.d.* fluticasone propionate) on pulmonary function, exacerbations and health status in 751 patients with moderate-to-severe COPD (mean FEV₁ 50% pred). At the end of the 3-yr follow-up, there was no significant benefit of ICS *versus* placebo with respect to the annual rate of decline in FEV₁. However, the mean exacerbation rate was reduced by 25%, from 1.32·yr⁻¹ on placebo to 0.99·yr⁻¹ with fluticasone propionate. Similarly, health status deteriorated by 3.2 units·yr⁻¹ on placebo *versus* 2.0 units on fluticasone propionate (fig. 4). In addition, withdrawals from the study due to nonmalignant respiratory diseases occurred more often in the placebo group than with ICS (25 *versus* 19%) [40]. Thus, while ICS did not slow the rate of decline of FEV₁ in the long-term ISOLDE study, it did significantly improve respiratory and overall health *versus* placebo. However, the relatively limited magnitude of improvements led to the question of whether the addition of a long-acting β₂-agonist could improve the results, as a consequence of molecular interactions between these products [41]. The TRial of Inhaled STeroids ANd long-acting β₂-agonists (TRISTAN) compared the efficacy of the combination of a long-acting β₂-agonist (50 µg salmeterol *b.i.d.*) and an ICS (500 µg fluticasone propionate *b.i.d.*) to the effects of either of the agents alone, in 1,465 patients with COPD. The primary outcome was FEV₁ at the end of 12 months of therapy. All active treatments improved lung function, symptoms and health status, and reduced use of rescue medication and frequency of exacerbations. Combination therapy improved pre-treatment FEV₁ significantly more than placebo, salmeterol or fluticasone. Perhaps more importantly, it was also significantly more effective than either single agent in improving health status [42]. Again, benefits were more obvious in patients with FEV₁ <50% pred. Similar results were found in 1-yr trials with the combination of budesonide and formoterol [43, 44].

Finally, in the TORCH trial, patients receiving the combined treatment had a St George's Respiratory Questionnaire score that was on average 3.1 units lower than those receiving placebo, 2.2 units lower than those receiving salmeterol monotherapy and 1.2 units lower than those receiving fluticasone monotherapy. Combined treatment was also associated with 25% fewer exacerbations than placebo, 12% fewer than salmeterol and 9% fewer than fluticasone [30].

Thus, even if their effects on the "conservatively defined" natural history of the disease can be debated, several pharmacological agents demonstrated their ability to provide clinically significant benefits in COPD patients. However, these effects remain of a relatively limited magnitude, making new, more effective treatments desirable and leading to consideration of the benefit/risk ratio of existing therapies before reaching a conclusion as to their interest.

SAFETY ISSUES WITH CURRENT PHARMACOLOGICAL TREATMENTS OF COPD

The combination of ICS and a long-acting β₂-agonist has demonstrated significant benefit in the management of patients with COPD, but there are still safety concerns about the long-term use of these treatments in this disease. A recent meta-analysis of safety results for ICS administered in the

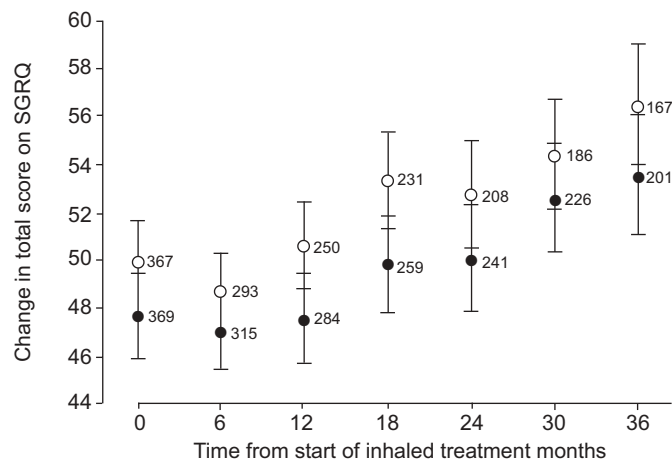


FIGURE 4. Effects of fluticasone propionate 500 µg *b.i.d.* or placebo on decline in health status indicated by increasing total scores on the St George's Respiratory Questionnaire (SGRQ; mean ± 95% confidence interval). The number at each assessment indicates the number of patients for whom measurements of health status were available at that visit. The study included 751 males and females aged 40–75 yrs with a mean forced expiratory volume in one second of 50% of the predicted normal. Health status deteriorated by 3.2 units·yr⁻¹ on placebo and 2.0 units·yr⁻¹ on fluticasone propionate ($p=0.0043$). ○: placebo; ●: fluticasone propionate. Reproduced and modified from [40] with permission from the publisher.

setting of clinical trials indicated negligible risk with these agents [16]. For example, pooled discontinuation rates did not differ significantly between ICS and placebo [16]. However, observational evidence suggests a dose-related risk of cataract and open-angle glaucoma in patients receiving ICS [16]. Results that address the possibility of an association between ICS and osteoporosis (which is also favoured by age, tobacco smoking and COPD itself) are mixed. A meta-analysis of randomised trials found no evidence of increased risk of loss of bone mineral density or fractures [16]. However, findings from two case-control studies suggested a relationship between ICS use and osteoporosis [16].

Recent results from patients treated in the Salmeterol Multi-centre Asthma Research Trial (SMART) have raised concerns about the safety of long-acting β₂-agonists. This study was discontinued because patients taking salmeterol (42 µg *b.i.d.*) had increased risk for mortality [45]. However, the increase in mortality was observed mainly in African-Americans. Thus, it may reflect a lower access to healthcare resources, poorer compliance to ICS treatment or a genetic susceptibility, rather than a general intrinsic toxicity of long-acting β₂-agonists. While it is not clear whether these findings can be generalised to individuals with COPD, they may raise some concern, since several of these patients suffered from cardiovascular comorbidities. However, a systematic review of the cardiovascular safety of salmeterol in COPD patients has provided reassuring results [46].

EMERGING THERAPIES

There has been great interest in the development of new therapies for COPD. COPD is characterised by chronic inflammation of the respiratory tract with increased numbers

of macrophages, neutrophils and cytotoxic T-lymphocytes in airways and the lung parenchyma. The central role of inflammatory processes in COPD and its comorbidities has focused research on mediators involved in recruitment and activation of inflammatory cells (most often neutrophils). Treatments aimed at inhibiting these inflammatory processes include phosphodiesterase 4 inhibitors (considered in the article by McIVOR [47] in the present issue of the *ERR*), nuclear factor- κ B inhibitors, adhesion molecule inhibitors, IL-10 and analogues, p38 mitogen-activated protein kinase inhibitors, phosphoinositide-3 kinase γ -inhibitors and immunomodulators [48]. Other new COPD treatments with potential anti-inflammatory properties currently in development include leukotriene B₄ antagonists, 5'-lipoxygenase inhibitors, IL-8 antagonists, MCP antagonists, TNF- α inhibitors, antioxidants and inducible nitric oxide synthase inhibitors. Treatments aimed at reducing oxidative stress in COPD have also been a focus of attention.

Other treatments have the potential to combat mucus hypersecretion, and there is also a search for serine proteinase and MMP inhibitors to prevent lung destruction and the development of emphysema [12, 49]. Finally, "repairing" agents, such as retinoic acid receptor agonists or stem cells, are also being studied.

CONCLUSIONS

At present, there is a large number of symptomatic treatments for COPD and these medications have been shown to significantly improve dyspnoea, exercise tolerance, activity, the rate of exacerbations and quality of life in patients with this disease. However, these agents may have limited efficacy in some patients, which is exacerbated by the fact that they are often used late in the course of disease, when the likelihood of reversible lesions may be reduced. Therapies that alter the course of COPD, as measured by survival and lung function decline, include smoking cessation, LTOT, and the combination of fluticasone propionate and salmeterol. However, the definition of a therapy that modifies the natural history of COPD may need to be revisited and more precisely defined in terms of markers and clinical outcomes indicative of progression, including the risks for comorbid extrarespiratory diseases. It is reasonable to suggest that early diagnosis and treatment of patients with COPD might be the first and potentially most important disease-modifying intervention, since it would result in the application of existing treatments at the time when they are most likely to provide their greatest benefits. This remains to be formally demonstrated.

Nevertheless, treatments with a more favourable long-term benefit/risk ratio are warranted. Their development will probably require more specific targeting of the local and systemic inflammatory processes that give rise to the pulmonary and extrapulmonary manifestations of chronic obstructive pulmonary disease.

REFERENCES

- 1 Global Initiative for Chronic Obstructive Lung Disease. Executive summary: global strategy for the diagnosis, management, and prevention of COPD, 2006. www.goldcopd.com. Date last updated: November 2006. Date last accessed: June 19, 2007.
- 2 Weiss ST, DeMeo DL, Postma DS. COPD: problems in diagnosis and measurement. *Eur Respir J* 2003; 21: Suppl. 41, 4s–12s.
- 3 National Heart, Lung and Blood Institute. Morbidity and Mortality Chartbook. Bethesda, National Institutes for Health, National Heart, Lung and Blood Institute, 2000.
- 4 Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2002; 166: 329–332.
- 5 Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574–580.
- 6 Decramer M, De Benedetto F, Del Ponte A, Marinari S. Systemic effects of COPD. *Respir Med* 2005; 99: Suppl. B, S3–S10.
- 7 Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 347–360.
- 8 Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 4: CD003793.
- 9 Rennard SI. Inflammation in COPD: a link to systemic comorbidities. *Eur Respir Rev* 2007; 16: 91–97.
- 10 Chung KF. Cytokines as targets in chronic obstructive pulmonary disease. *Curr Drug Targets* 2006; 7: 675–681.
- 11 Lim S, Roche N, Oliver BG, Mattos W, Barnes PJ, Fan CK. Balance of matrix metalloprotease-9 and tissue inhibitor of metalloprotease-1 from alveolar macrophages in cigarette smokers. Regulation by interleukin-10. *Am J Respir Crit Care Med* 2000; 162: 1355–1360.
- 12 Roche N, Huchon G. Reducing airways inflammation to prevent exacerbations in chronic obstructive pulmonary disease. *Allergy* 2005; 60: 1350–1356.
- 13 Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J* 2003; 22: 672–688.
- 14 Sevenoaks MJ, Stockley RA. Chronic obstructive pulmonary disease, inflammation and co-morbidity - a common inflammatory phenotype? *Respir Res* 2006; 7: 1–9.
- 15 Rennard SI. Treatment of stable chronic obstructive pulmonary disease. *Lancet* 2004; 364: 791–802.
- 16 Gartlehner G, Hansen RA, Carson SS, Lohr KN. Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes. *Ann Fam Med* 2006; 4: 253–262.
- 17 Roche N, Lepage T, Bourcereau J, Terrioux P. Guidelines versus clinical practice in the treatment of chronic obstructive pulmonary disease. *Eur Respir J* 2001; 18: 903–908.
- 18 Schols AM, Wesseling G, Kester AD, et al. Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. *Eur Respir J* 2001; 17: 337–342.
- 19 Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994; 272: 1497–1505.
- 20 Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002; 166: 675–679.

- 21 Anthonisen NR, Skeans MA, Wise RA, *et al.* The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; 142: 233–239.
- 22 Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
- 23 Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. A clinical trial. *Ann Intern Med* 1980; 93: 391–398.
- 24 Gorecka D, Gorzelak K, Sliwinski P, Tobiasz M, Zielinski J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; 52: 674–679.
- 25 Chaouat A, Weitzenblum E, Kessler R, *et al.* A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. *Eur Respir J* 1999; 14: 1002–1008.
- 26 Anzueto A, Tashkin D, Menjoge S, Kesten S. One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. *Pulm Pharmacol Ther* 2005; 18: 75–81.
- 27 Sin DD, Man SF. Pharmacotherapy for mortality reduction in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; 3: 624–629.
- 28 Sin DD, Wu L, Anderson JA, *et al.* Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 992–997.
- 29 Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. *Eur Respir J* 2002; 20: 819–825.
- 30 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
- 31 Ferguson GT, Calverley PMA, Anderson JA, *et al.* Effect of salmeterol/fluticasone propionate (SFC) on bone mineral density (BMD) and eye disorders over three years in the TORCH trial. *Am J Respir Crit Care Med* 2007; 175: A763.
- 32 Leidy NK. Evolving concepts in the measurement of treatment effects. *Proc Am Thorac Soc* 2006; 3: 212–217.
- 33 Rennard SI. Chronic obstructive pulmonary disease: linking outcomes and pathobiology of disease modification. *Proc Am Thorac Soc* 2006; 3: 276–280.
- 34 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA. Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study. *Thorax* 2003; 58: 654–658.
- 35 Wolkove N, Dajczman E, Colacone A, Kreisman H. The relationship between pulmonary function and dyspnea in obstructive lung disease. *Chest* 1989; 96: 1247–1251.
- 36 Taube C, Lehnigk B, Paasch K, Kirsten DK, Jorres RA, Magnussen H. Factor analysis of changes in dyspnea and lung function parameters after bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 216–220.
- 37 Hatipoglu U, Laghi F, Tobin MJ. Does inhaled albuterol improve diaphragmatic contractility in patients with chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 1999; 160: 1916–1921.
- 38 Jones PW, Agusti AG. Outcomes and markers in the assessment of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27: 822–832.
- 39 Casaburi R, Mahler DA, Jones PW, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–224.
- 40 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
- 41 Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. *Eur Respir J* 2002; 19: 182–191.
- 42 Calverley P, Pauwels R, Vestbo J, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449–456.
- 43 Szafranski W, Cukier A, Ramirez A, *et al.* Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21: 74–81.
- 44 Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 912–919.
- 45 Nelson HS, Weiss ST, Blecker ER, *et al.* The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; 129: 15–26.
- 46 Ferguson GT, Funck-Brentano C, Fischer T, Darken P, Reisner C. Cardiovascular safety of salmeterol in COPD. *Chest* 2003; 123: 1817–1824.
- 47 McIvor RA. Future options for disease intervention: important advances in phosphodiesterase 4 inhibitors. *Eur Respir Rev* 2007; 16: 105–112.
- 48 Barnes PJ, Stockley RA. COPD: current therapeutic interventions and future approaches. *Eur Respir J* 2005; 25: 1084–1106.
- 49 Barnes PJ, Hansel TT. Prospects for new drugs for chronic obstructive pulmonary disease. *Lancet* 2004; 364: 985–996.