Formoterol in the management of chronic obstructive pulmonary disease

Paschalis Steiropoulos
Argyris Tzouvelekis
Demosthenes Bouros

Department of Pneumonology,
University Hospital
of Alexandroupolis, Greece

Abstract: Bronchodilators represent the hallmark of symptomatic treatment of Chronic Obstructive Pulmonary Disease (COPD). There are four categories of bronchodilators: anticholinergics, methylxanthines, short-acting β_2-agonists, and long-acting β_2-agonists such as formoterol. Significant research has been performed to investigate the efficacy, safety and tolerability of formoterol in the therapeutic field of COPD. Formoterol exhibits a rapid onset of bronchodilation similar to that observed with salbutamol, yet its long bronchodilatory duration is comparable to salmeterol. In addition, formoterol presents with a clear superiority in lung function improvement compared with either ipratropium bromide or oral theophylline, while its efficacy improves when administered in combination with ipratropium. Formoterol has been shown to better reduce dynamic hyperinflation, which is responsible for exercise intolerance and dyspnea in COPD patients, compared with other bronchodilators, whereas it exerts synergistic effect with tiotropium. Moreover, formoterol reduces exacerbations, increases days free of use of rescue medication and improves patients' quality of life and disease symptoms. Formoterol has a favorable safety profile and is better tolerated than theophylline. Collectively, data extracted from multicenter clinical trials support formoterol as a valid therapeutic option in the treatment of COPD.

Keywords: chronic obstructive pulmonary disease, formoterol, long-acting β_2-agonists

Introduction

Chronic obstructive pulmonary disease (COPD) affects more than 5% of the adult population and represents the fourth leading cause of death worldwide with a progressively increasing mortality and morbidity (Murray and Lopez 1997; Coultas et al 2001). Approximately 2.75 million deaths per year are caused by COPD, and the number is expected to increase. It is estimated that by the year 2020 COPD will be the third-leading cause of death and the fifth leading cause of disability worldwide (Sullivan et al 2000; Michaud et al 2001). The traditional understanding of the pathogenesis of COPD has focused on the presence of chronic airflow obstruction, which is slowly progressive and not fully reversible, and therefore the main therapeutic approach has been directed to relieve this. However, more recently it has been understood that airflow limitation is associated with an abnormal inflammatory response which appears to be responsible for the combination of small airway disease and architectural distortion of the lung parenchyma, the mucociliary dysfunction, and some systemic effects which include skeletal muscle dysfunction, nutritional abnormalities, weight loss, cardiovascular and nervous system abnormalities, and osteoskeletal effects such as osteoporosis (Oudijk et al 2003; Agusti 2005).

Spirometry provides the most common quantitative assessment of pulmonary function and is an essential tool in the diagnosis and monitoring of COPD. The most recent update of Global Initiative for Chronic Obstructive Lung Disease (GOLD) (National Heart, Lung, and Blood Institute 2006) classifies COPD severity into four groups according to spirometric results and proposes the proper treatment for each

Correspondence: Demosthenes E Bouros
Department of Pneumonology,
University Hospital of Alexandroupolis,
Alexandroupolis 68100, Greece
Tel/Fax +30 25510 76106
Email bouros@med.duth.gr

stage. Bronchodilators represent the hallmark of symptomatic treatment of COPD. There are four categories of bronchodilators: anticholinergics, methylxanthines, short-acting β_2-agonists, and long-acting β_2-agonists. As-needed use of a short-acting bronchodilator may be sufficient for patients with mild disease (stage I), whereas treatment with a long acting bronchodilator or a combination may be necessary in moderate to severe disease (stages II-IV).

The current pharmacological therapy for COPD is limited in its ability to modify the progressive decline in lung function, a hallmark of COPD, and to reduce its mortality, which is associated with progressive disease, as was recently reported by the trial Towards a Revolution in COPD Health (TORCH) where the reduction in mortality failed to reach statistical significance (Calverley et al 2007).

In the absence of available drugs preventing the evolution of the disease, the key aims for improving therapeutic outcomes are: to reduce symptoms, especially dyspnea, to improve exercise capacity, to reduce exacerbations and the possible need for hospitalization, and to enhance health status and improve quality of life (Mahler 2002). In line with these, experts state that the management of a stable COPD patient includes several clear steps: a) reduction of risk factor exposure by smoking cessation, b) optimizing expiratory flow by the use of bronchodilator drugs, such as long-acting β_2-agonists (LABAs) including formoterol and salmeterol, and anticholinergic agents such as tiotropium and ipratropium, c) reducing pulmonary inflammation most commonly by corticosteroids, and d) preventing and managing acute exacerbations (Calverley 2001; Sin et al 2003). In addition there is mounting evidence supporting the cardinal contribution of domiciliary oxygen treatment and pulmonary rehabilitation in ameliorating quality of life of patients developing exertional breathlessness. Surgical therapy (lung reduction for emphysematic patients) has a role in more advanced disease, whereas ventilatory support either acutely or chronically using non-invasive means has been studied and their utility in hypercapnic subjects has been clearly demonstrated (Plant et al 2000).

The scope of this review article is to summarize the current state of knowledge regarding the efficacy, safety, and tolerability of inhaled formoterol in the management of COPD and present some of the future perspectives focused on quality of life, patient satisfaction and drug uptake.

Pharmacodynamic – pharmacokinetic properties

The pharmacologic properties of formoterol have been reviewed previously (Faulds et al 1991; Bartow and Brogden 1998). Briefly, inhaled formoterol is a long-acting β_2-agonist, with rapid onset (5 minutes in single- and multiple-dose studies) that maintains a bronchodilator effect for at least 12 hours. All β_2-agonists are active on β_2-adrenoreceptors of smooth muscles of the bronchi, resulting in their relaxation, and therefore their bronchodilation. β_2-agonists also drastically inhibit systemic inflammatory response or local cell proliferation (Johnson and Rennard 2001).

The pharmacodynamic effects of formoterol are mediated through activation of intracellular adenyl cyclase, which catalyzes the conversion of ATP to cyclic adenosine monophosphate (cAMPi) (Foradil 2004). All β_2-agonists have the ability to increase heart rate and plasma glucose levels, and to cause hypokalemia by shifting potassium within cells. In addition these agents may increase levels of serum insulin, lactate acid, pyruvate acid, and free fatty acids when used in higher doses. In a double-blind placebo-controlled trial, Guhan et al (2000) showed dose-dependent increases in heart rate, corrected QT interval, and serum glucose levels, and dose-dependent decreases in plasma potassium concentrations with inhaled formoterol 24–96 μg or salmeterol 100–400 μg.

The maximum plasma concentration of formoterol (92 ng/L) is reached within 5 minutes of inhalation of a single supraoptimal dose of it (120 μg). Urinary excretion findings showed that the absorption in the lungs was linear with inhaled formoterol 12–96 μg in a study with 12 healthy volunteers. Moreover, in vitro plasma protein cleavage of formoterol was 61%–64% at concentrations 0.1–100 μg/L. Mean plasma concentrations of the drug at 10 minutes to 6 hours post-inhalation are 4.0–8.8 ng/L and 8.0–17.3 ng/L, respectively, after multiple doses of formoterol 12–24 μg bid for a period of 12 weeks in COPD patients (Cazzola et al 1994; Cheer and Scott 2002).

Formoterol is metabolized primarily in the liver by four cytochrome P450 (CYP) isoenzymes. These enzymes are not inhibited by the drug at therapeutic concentrations. Following inhalation of the drug in dose regimens of 12–24 μg by 18 COPD patients, 7% of the overall dose was finally excreted in the urine as unchanged drug and 6%–9% of the total dose was cleaved as direct conjugates of formoterol. The mean terminal cleavage half-life was about 10 hours following inhalation of formoterol 120 μg by 12 healthy volunteers. Unfortunately, so far, there are no pharmacokinetic data for the use of formoterol in patients with hepatic or renal failure or impairment or in elderly individuals (Bartow and Brogden 1998; Cheer and Scott 2002).

Efficacy of the formoterol in COPD treatment

Improvement in lung function parameters

Formoterol, both as a pressurized metered dose inhaler (pMDI) or a dry powder inhaler (DPI) formulation, has demonstrated its efficacy in the treatment of COPD and has been investigated in numerous clinical studies. These studies have examined single- or multiple-dose administration and have utilized a number of outcomes, which relate not only to lung function parameters, but also to symptoms, exacerbations, health-related quality of life (HRQoL), and exertion capacity. These outcomes have been considered in the context of primary, confirmatory analyses (mainly FEV_1), but also in the context of secondary exploratory analyses. As a word of caution, when multiple secondary outcomes are investigated, a random misleading result cannot be robustly excluded (Kottakis et al 2001; Friedman et al 2002).

Fast onset of bronchodilatory action

Kottakis et al (2002) compared formoterol 12 and 24 μg, as dry powder for oral inhalation, with dry powder salmeterol 50 and 100 μg in a single-dose, cross-over study in patients with partially reversible, moderately severe, stable COPD; ΔFEV_1 following a standard dose of salbutamol was not in excess of 12% of patient's predicted normal value. Median time to a 12% change from baseline FEV_1 value was 5 min with both formoterol doses and 10 min with both salmeterol doses. This was in line with data generated in asthma studies that support a fast action comparable to that of salbutamol (Donohue 2004). In fact, Benhamou et al (2001) blindly compared the administration of 24 μg dry powder of formoterol in a single dose with 400 μg dry powder salbutamol in patients with severe COPD. Both active drugs demonstrated their fast onset of effect on FEV_1 in this patient population, both drugs producing similar bronchodilation within 5 min of dosing and during the ensuing 30 min. Improvement in FEV_1 from 5 min to 3 hours post-treatment was also similar with formoterol and salbutamol. Both drugs induced almost maximal bronchodilation by 30 min post-treatment, 80% of maximum effect occurring within 5 min.

This result was further corroborated in the study by Maesen et al (1999) in which single doses of 6 and 24 μg dry powder formoterol administered to poorly reversible COPD patients resulted in a modest increase in FEV_1. However, significant improvement, compared to placebo, was observed in the work of breathing (WoB) (>25%) and airway resistance (Raw) (>20%) within 10 min.

Long duration of bronchodilatory action

In the same study (Maesen et al 1999) the FEV_1 remained higher during the 12 post-dose hours after formoterol, compared with placebo. For the area under the FEV_1 curve (AUC) 0–12 hours post dose, a mean increase in FEV_1 of 50 mL was calculated for placebo, 120 mL for 6 μg and 230 mL for the 24 μg formoterol. These results over the 12-hour dosing interval may be considered as clinically important in a patient population with stable, poorly reversible COPD, as they exceed 100 mL for the 6 μg dose and the upper limit of the daily variability of the measurement for the 24 μg dose.

Only two studies have examined so far the effect of formoterol administered in multiple doses. Rossi et al (2002) compared 12 and 24 μg of formoterol given bid in patients with stable COPD, versus oral sustained-release theophylline bid; Dahl et al (2001) compared the same dosage of formoterol (12 and 24 μg bid) with 40 μg ipratropium bromide qid. Both studies were of a parallel group design with each patient receiving treatment for 12 months and 3 months, respectively. Both studies utilized a group of patients receiving placebo (ie, usual therapy) to facilitate the analyses. Both studies demonstrated 12 hours of bronchodilatory action that was significant and clinically meaningful over placebo and active comparators, and persisted over time.

Formoterol versus placebo

The vast majority of clinical studies have considered the effect of formoterol on FEV_1. These studies have, in most situations, utilized this marker of efficacy as the primary outcome, for which each corresponding study was powered. For a disease characterized by a relative fixed airflow obstruction, the utilization of FEV_1 to test for efficacy requires the inclusion of patients with at least some degree of FEV_1 reversibility. Therefore in these studies (Benhamou et al 2001; Kottakis et al 2002) an upper limit of FEV_1 change of not less than 12% of patent's predicted normal and a minimum of at least 5% of patient's baseline value following a standard dose of a short acting β_2-agonist was often used; other limits though have also been used (Maesen et al 1999; van Noord et al 2005). Resting lung volumes and capacities, especially those that predict the effect on dynamic hyperinflation, have also been used in a number of studies, as secondary efficacy outcomes (Bouros et al 2004; Di Marco et al 2006; van Noord 2006).

Three multicenter, randomized, placebo-controlled studies are currently evaluating the effect of formoterol on dynamic hyperinflation, a factor that often contributes to dyspnea and exercise intolerance in COPD patients. In addition

to FVC and FEV_1, indices related to dynamic hyperinflation such as inspiratory capacity (IC) are both reproducible and well correlated with exercise tolerance and dyspnea (Yan et al 1997). Di Marco and colleagues (2003) compared the acute effect of 4 inhaled bronchodilators, including formoterol, and placebo on IC, FEV_1, FVC, and dyspnea in 20 consecutive COPD patients. Patients underwent lung function tests and dyspnea evaluation at baseline and at 5 serial time points after drug or placebo administration. Results clearly demonstrated that patients with decreased baseline IC showed a statistically significant increase of IC, especially at 30 mins post-bronchodilation, which was highly correlated with improvement in dyspnea sensation at rest.

Formoterol versus other β_2-agonists

D'Urzo et al (2001) compared the addition of formoterol 12 μg bid to the addition of salbutamol 200 μg qid in COPD patients on ipratropium 40 μg qid. In this investigation a randomized double blind 2-period cross-over design was employed, with every patient treated for 3 weeks during each of the two treatment periods. Randomized patients presented with a limited reversibility of their airflow obstruction, of less than 200 mL following a standard salbutamol dose. The results showed that morning peak expiratory flow (PEF) and FEV_1 were significantly higher with the formoterol–ipratropium co-treatment compared with the salbutamol–ipratropium combination. Similar beneficial findings were noted in the symptom score, the percentage of days free of rescue drug, and the health status.

The impact of formoterol (12 μg) on IC in comparison with salmeterol (50 μg) was studied in 47 COPD patients (Bouros et al 2004). Findings further extended the superiority of formoterol compared with salmeterol in acutely improving (over the first hour post-dose) indices of dynamic hyperinflation in COPD patients with low baseline IC, an observation in line with the faster onset of bronchodilation exhibited by formoterol.

Vervloet et al (1998) conducted a 6-month study in 482 COPD patients on regular treatment with inhaled corticosteroids (ICS). Patients received either formoterol 12 μg bid or salmeterol 50 μg bid. Improvements in morning predose PEF were similar in both groups while patients on formoterol experienced superior improvements in evening predose PEF rates.

Formoterol versus anticholinergics

Ipratropium

Sichletidis et al (1999) compared the bronchodilatory responses to formoterol 12 μg and 24 μg versus ipratropium bromide 40 μg and their combination in 27 patients with COPD. Intriguingly, effects of formoterol in FEV_1 were similar to the combination of the two agents and highly superior to ipratropium alone.

Two years later, Dahl et al (2001) clearly demonstrated in a large series of 780 patients that formoterol (12 and 24 μg bid) had faster onset and longer duration of action than ipratropium bromide (40 μg qid) and was more effective in terms of increases in FEV_1, reductions in symptoms scores, and improvements in health status and exacerbations over a 12-week treatment period.

Tiotropium

Cazzola et al (2004) looked for an additive effect between tiotropium and formoterol in a double-blind and double-dummy, single-dose, cross-over clinical study, in 20 patients with stable COPD. Tested were single doses of 12 μg formoterol, 18 μg tiotropium, and the combination of these doses. Changes in FEV_1 10 minutes after inhalation were statistically greater with formoterol than with tiotropium. At the same time point, combination of formoterol – tiotropium was also superior to tiotropium alone, but not to formoterol alone. Rise in FEV_1 was achieved in 38 minutes by formoterol versus 79 minutes by tiotropium. For maximum increase in mean FEV_1, arithmetic differences in favor of the combination of the two bronchodilators failed to achieve statistical significance versus the monotherapies (0.192 L for formoterol, 0.176 L for tiotropium, 0.210 L for the combination). No statistical significance was observed in average FEV_1. However, at 24 hours the mean FEV_1 value was still statistically significantly higher than the pre-dosing value following tiotropium and the combination, but not with formoterol alone (0.084 L after tiotropium, 0.088 L after tiotropium + formoterol, 0.058 L after formoterol alone).

The statistical significance that was not achieved in the Cazzola et al single dose study, was shown in a multiple dose, 3-way cross-over study in stable COPD patients, 2 weeks duration per treatment period, by Van Noord et al (2006). In this study, monotherapy with tiotropium was compared with combinations of tiotropium plus formoterol once, or twice daily. The addition of formoterol was superior to tiotropium alone in average FEV_1 during the 24-hour period. Additionally, authors showed that the add-on formoterol dose of 12 μg in patients receiving tiotropium improved resting IC as well as in FVC and FEV_1 for more than 12 hours. Addition of a second dose of formoterol further increased IC and FVC for a time period that did not exceed 12 hours.

Di Marco et al (2006) investigated the effect of single doses of formoterol (12 μg), tiotropium (18 μg), and their combination in 21 patients experiencing an acute exacerbation of COPD. Differences in peak FEV_1 and FVC, and 24-hour average FEV_1 and FVC were not recorded between the monotherapies, with the combination of the two achieving a significant advantage over the monotherapies. More important, a bronchodilating action was evident at 24 hours only with the combination of the two bronchodilators.

Formoterol versus theophylline

In the study by Rossi et al (2002), formoterol (12 μg bid) was found to improve statistically FEV_1 AUC at 3 and 12 months. This beneficial effect was also observed with formoterol 24 μg twice daily after 3 months. Both doses were superior to theophylline for FVC AUC at 3 months.

Improvement in symptoms and the need for rescue medication

The published guidelines of the Global Initiative for COPD recommend that bronchodilator medications be prescribed to COPD patients for relief of symptoms (National Heart, Lung, and Blood Institute 2006). The classic symptoms of COPD are chronic cough, excessive sputum production, and dyspnea, which is the main reason for consultation with the primary care physician and a major cause of disability and anxiety (Mahler 2002). Although, FEV_1 has been widely used as a surrogate marker for dyspnea, many studies have documented ameliorations in dyspnea without any accompanying spirometry improvement (Guyatt et al 1987, 1989; Mahler et al 1995).

Dahl et al (2001) performed a multicenter, double blind, randomized placebo-controlled study and compared the efficacy of formoterol and ipratropium bromide in 740 COPD patients by assessing disease symptoms with a patient diary that recorded the use of rescue medication and a series of 6 parameters on a 4-point scale. Symptoms that were evaluated included ability to perform usual daily activity, breathlessness over the previous 24 hours and on rising, night awakenings due to respiratory symptoms, and cough and sputum production. In contrast to ipratropium, both doses of formoterol (12 and 24 μg) significantly improved symptom scores and significantly reduced the use of rescue drugs compared with placebo over a 12-week period. Results were substantiated by Campbell et al in a study evaluating the efficacy and tolerability of formoterol compared to placebo, using as primary endpoints lung function parameters and COPD symptoms (Campbell et al 2005). The overall treatment period represents the most important caveat of this study due to the fact that it may be considered too short to capture a significant number of disease deteriorations and to evaluate parameters such as daily symptoms and rescue use that need to be addressed on a longitudinal basis.

With this aim in mind, Rossi et al (2002) used a similar patient diary with the same six parameters to evaluate the effectiveness of formoterol (12 and 24 μg) compared with oral theophylline or placebo in improving daily symptoms over a 12-month treatment period. Although symptom scores at 3-month intervals tended to be lower in patients receiving formoterol 12 or 24 μg than in the placebo group, differences failed to reach statistical significance. A type II error cannot be excluded; however, the exact reason for this discrepancy remains unknown. Furthermore, authors reported that both formoterol doses, compared with the placebo group, exhibited significant decrement in the mean number of puffs of rescue medication and increment in the percentage of days free of rescue drug over the entire treatment period.

In the study by D'Urzo et al (2001) COPD patients receiving ipratropium 40 μg qid reported lower scores in symptoms such as coughing, breathlessness, and sputum production when formoterol 12 μg × 2 was added instead of salbutamol 200 μg × 4. Moreover, formoterol instead of salbutamol resulted in fewer puffs/day of rescue medicine, and more days with no use of rescue drug.

Improvement in COPD exacerbations

In the study by Rossi et al (2002), which compared the efficacy of formoterol versus theophylline or placebo, formoterol (either 12 μg or 24 μg daily) was superior in preventing mild exacerbations. Daily use of 24 μg of formoterol resulted in statistically less need for additional therapy (antibiotics, corticosteroids, or oxygen). The need for COPD-related hospitalization was observed to be 4 times higher in the placebo group compared with the formoterol 24 mg group, and 2 times higher in the 12 mg group. These results confirmed those by Dahl et al (2001) which showed that frequency of mild exacerbations was significantly lower in patients with formoterol versus placebo.

Formoterol seems to be superior to salbutamol for COPD exacerbations, since more patients denied having exacerbations (D'Urzo et al 2001). Even mild exacerbations ('bad days') were less in this group.

Improvement in health-related quality of life (HRQoL)

One of the major clinical outcomes measured in evaluating the responses to pharmacotherapy in patients with COPD

include health status. The Chronic Respiratory Disease Questionnaire (Guyatt et al 1987) and the St George's Respiratory Questionnaire (SGRQ) (Jones et al 1992), specific measurement tools used widely in multicenter clinical trials with the disease, are the best and most reliable ways of recording treatment response. In addition, the generic Medical Outcomes Short Form-36 (SF-36) questionnaire (Ware et al 1992) can reflect changes in HRQoL among patients receiving therapy.

SGRQ was used as a secondary efficacy variable in all the aforementioned large multicenter studies. A change of 4 points from baseline was considered statistically significant, indicating an important difference for the patient. The questionnaire was administered before the first dose of the study and at the end of the treatment period. In the study by Dahl et al (2001), COPD patients received a beneficial effect for SGRQ total score with both formoterol dose regimens (12 and 24 μg). These patients also had also statistically and clinically significant improvements in the symptoms, activity, and impacts domains, as mentioned above. The latter results were further extended in the other multicenter clinical trial by Rossi et al (2002) and beneficial effect was sustained over a longer treatment period of time (12 months).

The above observations give credence to the view that LABAs, including formoterol, not only improve lung function by relaxing bronchial smooth muscle but may also provide clinical benefits that can be proven cardinal to symptomatic COPD patients.

Improvement in inflammatory markers

COPD is associated with chronic inflammatory response in the lungs. Elevation of neutrophil count is detected in sputum, and of macrophage count in lung parenchyma and in bronchoalveolar lavage (National Heart, Lung, and Blood Institute 2006). Increased CD4+ and CD8+ cell counts and an elevation of CD8+:CD4+ ratio are also observed. Additionaly, B-lymphocytes are increased, along with epithelial cells, and eosinophils. The latter is detected during exacerbations (National Heart, Lung, and Blood Institute 2006).

Animal experimental models for COPD have demonstrated that long acting β_2-agonists influence neutrophil count and function (Johnson and Rennard 2001) while Bowden et al (1994) showed formoterol to be effective in inhibiting neutrophil adhesion in the airway mucosa of the rats. In other studies performed in vitro, formoterol has inhibited activated neutrophil oxidant generation (Anderson et al 1996), leucotriene release (Rabe et al 1993), and superoxide anion generation (Okada et al 1993) from guinea pig eosinophils.

Efficacy of combination with inhaled steroids therapy

The synergistic effect of ICS combined with long-acting β_2-agonists has been suggested for COPD as well as for asthma. Two fixed combinations are currently available: salmeterol–fluticasone and formoterol – budesonide. The current management guidelines (National Heart, Lung, and Blood Institute 2006) recommend addition of an ICS to bronchodilator therapy for COPD patients with an FEV_1 $<$50% predicted, who experience repeated exacerbations. No important difference between the two combinations in the recommended dosages was reported by Cazzola et al (2003) in patients with COPD.

In a 12-month, randomized, double-blind, placebo-controlled, parallel study, the combination of formoterol with budesonide (formoterol 6 μg – budesonide 200 μg) administration was compared with that of the individual agents (formoterol 6 μg, budesonide 200 μg) and of placebo in terms of efficacy and safety (Szafranski et al 2003). Medication was administered via two inhalations twice daily. The aim of this study was to examine the efficacy and safety of the combination of formoterol/ budesonide against placebo and monocomponents in terms of FEV_1 changes and numbers of exacerbations. In addition, other parameters such as FVC, PEF, HRQoL, symptoms, and use of relieve medication were recorded. This study concluded that the combination of the two agents increased FEV_1 by 15% vs placebo, and 1% vs. formoterol alone; and reduced by 24% the number of exacerbations vs placebo. Also impressive were the effects of formeterol – budesonide combination vs placebo on the number of exacerbations, total symptom score, days free of shortness of breath, nights free of awakenings, use of reliever medication, and HRQoL scores.

A related trial by Calverley et al (2003) studied the maintenance of clinical improvement over a longer period in COPD patients under inhaled therapy and investigated which drugs were responsible for patients well being. The primary outcomes were time to first exacerbation and change in FEV_1. This study demonstrated that the combination of formoterol and budesonide provided effective maintenance therapy over 12 months. A reduced withdrawal in the combination therapy group, due to worsening of COPD, than in the monotherapy groups was recorded. Combination treatment also prolonged the time to first COPD exacerbation and significantly improved

SGRQ total scores and use of rescue medications compared with monotherapy with formoterol or budesonide.

Safety and tolerability

Long-acting β_2-agonists are generally considered to be well tolerated, and a low incidence of adverse events has been reported across all the clinical studies conducted (Table 1). A wide clinical experience has been gained on the use of formoterol in patients with asthma. In some of these studies, formoterol has been evaluated at doses higher than therapeutic, showing a good safety profile. It has been however important to evaluate whether the agent is also safe in COPD patients, in light of possible complicating factors such as age and concomitant disorders.

In a study by Dahl et al (2002) comparing the efficacy and safety of formoterol at doses of 12 μg (F12) and 24 μg (F24) twice daily versus placebo and ipratropium bromide in 780 COPD patients over a 12-week treatment period, the incidence of adverse events was similar in all the treatment groups, as well as the proportion of patients reporting adverse events considered drug-related by the investigator (11% on 12 μg, 19% on 24 μg, 12% on placebo and 12% on ipratropium). The most frequent drug-related adverse events were headache, tremor, dry mouth, muscle cramps, coughing, COPD exacerbations, dyspnea, and pruritus. Cardiovascular events and heart rhythm disorders were uncommon across all the treatment groups (respectively, 1 and 6 on 12 μg, 2 and 4 on 24 μg, 5 and 8 on placebo, and 5 and 8 on ipratropium). There was a low incidence of clinically relevant abnormal serum potassium and glucose, with no difference among treatment groups, but most importantly no deaths were recorded in this study.

In this respect, the safety of formoterol use as monotherapy in COPD patients has been good in all clinical trials conducted compared with placebo, ipratropium, and other β_2-agonists and formoterol were better tolerated than theophylline. Only a small proportion of patients experienced significant systemic adverse reactions.

In the study of Aalbers et al (2002) 3 different doses of formoterol DPI (4.5–9–18 μg twice daily) and placebo were administered to 690 patients with COPD during a 12-week treatment period. The most commonly reported adverse events were deterioration of COPD and respiratory infections, both present with a similar incidence in all the treatment groups (including placebo). No other adverse events occurred in >5% of patients.

Results of a 6-month safety and efficacy comparison of formoterol and salmeterol (Vervloet et al 1998) reported that both drugs were well tolerated and that adverse events were in similar proportions in both treatment groups. However, salmeterol has been associated with airway hyperresponsiveness (Sears 2002) and deterioration of lung function in children with asthma (Verberne et al 1997).

Similar findings were obtained in the study of Rossi et al (26) evaluating the efficacy and safety of formoterol at the doses of 12 μg and 24 μg twice daily versus placebo and oral slow-release theophylline in 854 COPD patients during a 12 months' treatment. The most common adverse events occurred with a similar incidence in all treatment groups (including placebo). The incidence of adverse events considered as drug-related by the investigator, was similar in the 12 μg and 24 μg formoterol and in the placebo groups (9% on F12, 8% on F24 and 8% on placebo), and higher in patients treated with oral slow-release theophylline (32%).

Discontinuations due to adverse events (COPD-related and not COPD-related) were from 2- to 4-fold more frequent in patients treated with theophylline, compared with the other groups. Four deaths occurred in the study (3 on 12 μg and 1 on 24 μg); however, only one case (myocardial infarction with rupture of the interventricular cardiac septum) was considered possibly related to study drug, while the others were considered not related to study drug (1 suicide, 1 post-traumatic death, 1 possible myocardial infarction).

In two other studies in which formoterol was administered at 9 μg bid (corresponding to a metered dose of 12 μg bid) in comparison with placebo, budesonide, and the fixed combination budesonide – formoterol for 12 months, the safety profile was similar to what previously known (Calverley et al 2003; Szafranski et al 2003). No further safety issues were noticed while the most commonly reported adverse events were deterioration of COPD and respiratory infection. The number of serious adverse events and deaths in the two studies did not show a relevant treatment-related pattern. Tachycardia and tremor, known as class effects of β_2-agonists, were reported in a very low proportion of patients (15%–3%) with no evident dose relationship.

Discussion

According to Global Initiative for COPD (National Heart, Lung, and Blood Institute 2006), long-acting bronchodilators are central to symptom management in COPD, are prescribed on an as-needed or on a regular basis to prevent or to reduce symptoms, and are convenient and effective, whereas their combination may improve efficacy and reduce side effects compared with increasing the dose of a single bronchodilator. Recent clinical trials attribute the impact of formoterol in the treatment of COPD mainly to the distinctive, rapid

Table 1 Most commonly reported adverse events

Formoterol	4.5 µg		9 µg		12 µg	18 µg		24µg	placebo		
Author	**Aalbers et al 2002**	**Calverley et al 2003**	**Aalbers et al 2002**	**Calverley et al 2003**	**Rossi et al 2002**	**Aalbers et al 2002**	**Calverley et al 2003**	**Rossi et al 2002**	**Aalbers et al 2002**	**Calverley et al 2003**	**Rossi et al 2002**
Subjects n	171	255	169	257	211	178	254	214	174	256	220
Deterioration of COPD	7 (4)	NA	12 (7)	NA	NA	18 (10)	NA	NA	16 (9)	NA	NA
Respiratory infection	21 (12)	33 (13)	24 (14)	34 (13)	NA	17 (10)	36 (14)	NA	18 (10)	24 (9)	NA
Chest pain	1 (1)	6(2)	2 (1)	4 (2)	NA	5 (3)	8 (3)	NA	2 (1)	5 (2)	NA
Back pain	1 (1)	6(2)	4 (2)	4 (2)	NA	4 (2)	8 (3)	NA	3 (2)	7 (3)	NA
Headache	4 (2)	NA	3 (2)	NA	13 (6)	4 (2)	NA	8 (4)	8 (5)	NA	20 (9)
Hyperglycemia	NA	NA	2 (1)	NA	NA	3 (2)	NA	NA	NA	NA	NA
Hypertension	NA	NA	3 (2)	NA	NA	3 (2)	NA	NA	3 (2)	NA	NA
Pain	9 (5)		1 (1)	NA	NA	3 (2)	NA	NA	2 (1)	NA	NA
Pharyngitis	3 (2)	8(3)	5 (3)	5 (2)	NA	3 (2)	7 (3)	NA	4 (2)	5 (2)	NA
Tachycardia	NA	NA	5 (3)	NA	NA	3 (2)	NA	NA	NA	NA	NA
Tremor	1 (1)		1 (1)	NA	1 (1)	3 (2)	NA	4 (2)	NA	NA	2 (1)
Fever	NA	11(4)	NA	9 (4)	NA	NA	36 (14)		NA	2 (1)	NA
Dyspnea	NA	12(5)	NA	5 (2)	12 (6)	NA	5 (2)	13 (6)	NA	5 (2)	11 (5)
Pneumonia	NA	7(3)	NA	5 (2)	NA	NA	8 (3)	NA	NA	2 (1)	NA
Rhinitis	NA	6(2)	NA	3 (1)	NA	NA	11 (4)	NA	NA	1 (<0.5)	NA
Dysphonia	NA	1(<0.5)	NA	5 (2)	NA	NA	5 (2)	NA	NA	1 (0.5)	NA
Moniliasis	NA	2(1)	NA	4 (2)	NA	NA	4 (2)	NA	NA	NA	NA
Viral Infection	NA	NA	NA	NA	34 (16)	NA	NA	31 (15)	NA	NA	39 (18)
COPD Exacerbation	NA	NA	NA	NA	34 (16)	NA	NA	26 (12)	NA	NA	33 (15)
Bronchitis	NA	NA	NA	NA	21 (10)	NA	NA	21 (10)	NA	NA	20 (9)
URTI	NA	NA	NA	NA	20 (10)	NA	NA	14 (7)	NA	NA	16 (7)
Insomnia	NA	NA	NA	NA	3 (1)	NA	NA	1 (1)	NA	NA	5 (2)
Dyspepsia	NA	NA	NA	NA	2 (1)	NA	NA	3 (1)	NA	NA	3 (1)
Abdominal pain	NA	NA	NA	NA	1 (1)	NA	NA	8 (4)	NA	NA	9 (4)
Nausea	NA	NA	NA	NA	1 (1)	NA	NA	1 (1)	NA	NA	4 (2)
Vomiting	NA	NA	NA	NA	1 (1)	NA	NA	1 (1)	NA	NA	NA

Note: data are presented as number of adverse events with % of patients reporting in parentheses.
Abbreviation: URTI, upper respiratory tract infection.

Table 2 Clinical trials on formoterol in COPD patients

Author	Patients enrolled	Mean age (years)	Treatment
Cazzola et al 1994	16	64.3	F 24 μg SLM 50 μg ALB 200 μg PL
Cazzola et al 1995	12	62.5	F 12 μg F24 μg SLM 50 μg
Vervloet et al 1998	482	48	F 12 μg BID SLM 50 μg BID
Celik et al 1999	22	57.3	F 12 μg SLM 50 μg PL
Maesen et al 1999	12	61	F 6 μg F 24 μg PL
Sichletidis et al 1999	27	64.7	F 12 μg F 24 μg IPR 40 μg IPR 80 μg F 12 μg + IPR 40 μg PL
Benhamou et al 2001	24	61.6 ± 7.8	F 24 μg ALB 400 μg PL
Cazzola et al 2001	16	65.6	F 12 μg F 24 μg ALB 400 μg ALB 800 μg PL
Dahl et al 2001	780	63.7	F 12 μg BID F 24 μg BID IPR 40 μg QID PL
D'Urzo et al 2001	159	65	F 12 μg BID + IPR 40 μg QID SLM 200 μg + IPR 40 μg QID
Aalbers et al 2002	692	62.4	F 4.5 μg BID F 9 μg BID F 18 μg BID PL
Cazzola et al 2002	20	60.6	F 9 μg ALB 100 μg F 18 μg ALB 200 μg
Kottakis et al 2002	47	63.5	F 12 μg F 24 μg SLM 50 μg SLM 100 μg PL
Rossi et al 2002	854	63	F 12 μg BID F 24 μg BID
Di Marco et al 2003	20	65	F 12 μg ALB 200 μg SLM 50 μg OXITR 200 μg PL
Bouros et al 2004	47	63.5	F 12 μg F 24 μg SLM 50 μg SLM 100 μg PL
Cazzola et al 2004	20	70.7	F 12 μg TIO 18 μg F 12 μg + TIO 18 μg
Campbell et al 2005	657	60	F 9 μg BID + TER 0.5 mg prn F 9 μg BID + F 4.5 μg prn PL + TER 0.5 mg prn
Di Marco et al 2006	21	72	F 12 μg BID TIO 18 μg QID F 12 μg BID + TIO 18 μg QID

Abbreviations: BID, twice daily; F, formoterol; IPR, ipratropium; OXITR, oxitropium, QID, 4 times daily; PL, placebo, SLM, salmeterol; TER, terbutaline; THEO, theophylline; TIO, tiotropium.

onset, long-acting β_2-adrenoreceptor activity. Formoterol produces significant improvements within 5 minutes and these benefits are sustained for almost half of the day. It has a more rapid onset and longer duration of action than ipratropium bromide, and has clear superiority in terms of lung function and quality of life.

Furthermore, it provides significantly greater improvements in symptom control and need for reliever medication than ipratropium bromide. Formoterol is more effective than theophylline in reducing the number of COPD exacerbations and increasing the number of days without rescue medication, and is better tolerated. Data presented and reviewed in this paper support the notion that formoterol has therapeutic and safety profiles comparable to and sometimes superior even to those of current first-line agents for moderate COPD (Table 2). These results not only support its use as a first-line

therapy in COPD but also give credence to its administration in combination with ipratropium bromide in patients who are non-responders to a single bronchodilator.

Finally, although formoterol is not yet indicated for administration on an as-needed basis for patients with mild disease, its rapid onset of action coupled with data derived from a clinical trial (Cazzola et al 2001) support its "on-demand" use, indicating it as a promising candidate for patients suffering from acute exacerbations of partially reversible COPD.

In conclusion, most studies reviewed in this paper have shown that formoterol has beneficial efficacy, safety, and tolerability profiles when administered in patients with COPD. Data extracted from multicenter clinical trials support formoterol as a valid therapeutic option in the treatment of COPD. Therefore, findings from the above studies need to be taken into consideration for future updates of guidelines for the management and treatment of this dismal disease.

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