Long-term effects of inhaled bronchodilators in stable chronic obstructive pulmonary disease

In chronic obstructive pulmonary disease (COPD) the inhaled bronchodilators represent the basis of the maintenance therapy, the therapeutic recommendations being made and adjusted based on the long-term therapeutic effects. This review focuses on the results of long-term (>1 year) studies with inhaled bronchodilators in COPD. Based on the data reviewed it can be concluded that long-acting bronchodilators such as tiotropium are most effective as individual therapy in milder COPD stages and also demonstrate added value when associated with other therapies in more advanced COPD stages. Long-acting β2 agonists are most effective not as standalone but when combined with inhaled corticosteroids for severe and very severe COPD stages. Despite the long-term efficacy and safety of inhaled long-acting bronchodilators being demonstrated in the existing studies, and despite these having contributed a great deal to a more appropriate positioning of such therapies in the management of stable COPD, several pending issues, such as long-term effects of combined bronchodilators regimens and of bronchodilators/corticosteroids triple combinations on disease outcome, remain to be documented by the subsequent studies.

KEYWORDS: COPD ■ inhaled bronchodilators ■ LABA ■ tiotropium

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Chronic obstructive pulmonary disease (COPD) is a disease of the lungs characterized by chronic inflammation of the airways and progressive airflow obstruction. Its main risk factor is smoking. The main clinical features are represented by limitation of exercise capacity and symptoms such as dyspnea, cough and sputum production, which aggravates as disease advances or during exacerbations.

In COPD the degree of airway obstruction defines its severity and classifies it in four stages.Apart from its clinical importance, this classification is also useful for therapeutic purposes (Table 1).

Existing management guidelines for stable COPD recommend a step-up approach according to disease severity apart from smoking cessation intervention, which is mandatory irrespective of the severity stage and wherever appropriate, inhaled bronchodilators, inhaled corticosteroids, pulmonary rehabilitation or long-term oxygen therapy [101].

The general aims of therapeutic regimen in stable COPD are represented by symptom relief, exacerbation and mortality rate reduction and health status improvement [101].

The scientific rationale for various pharmacological therapies in COPD was initially supported by their documented short-term efficacy evaluated in studies lasting less than 1 year, and further supported by documentation of their long-term effects. The latter category of effects are those assisting to a greater extent to improve therapeutic practice as they represent the basis of treatment guidelines. This was the case with inhaled corticosteroids, which were demonstrated to be not as effective in COPD as in asthma, and were evaluated in large-scale studies such as the EUROSCOP or ISOLDE, demonstrating their effect on reducing morbidity in more advanced COPD. Consequently, their use was recommended to be restricted only in patients with forced expiratory volume in 1 s (FEV)1%pred <50% with frequent exacerbations (Table 1) [1,2]. The data derived from these studies are frequently questioned nowadays but discussion of this is outside of the scope of this article.

Inhaled bronchodilators are the basis of pharmacological therapy in stable COPD; the short-acting formulations are currently preferred on an acute basis whereas long-acting compounds are currently recommended to be used regularly starting with moderate COPD stage. Their efficacy and safety are documented on both short- and long-term basis, but the aim of this article is to review the long-term effects of such compounds based on data derived from existing studies.

Inhaled anticholinergics

In stable COPD, inhaled anticholinergics have been used as a mainstay of bronchodilator therapy, short-acting formulations once used

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Table 1. Use of long-acting bronchodilators in stable chronic obstructive pulmonary disease therapy according to severity stage.

Inhaled medications	COPD stage			
	COPD stage I FEV1% pred > 80% FEV1/FVC < 70%	***COPD stage II FEV1% pred 50–80% FEV1/FVC < 70%***	***COPD stage III FEV1% pred < 50% FEV1/FVC < 70%***	***COPD stage IV FEV1% pred < 30% or FEV% pred 30–50% and chronic respiratory failure***
Short-acting bronchodilators: β2 agonists, anticholinergics	Rescue use			
Long-acting bronchodilators: β2 agonists, anticholinergics, alone or combined			Regular therapy	
Combination therapy: LABAs and inhaled corticosteroids				Regular therapy

COPD: Chronic obstructive pulmonary disease; LABA: Long-acting β2 agonists.
Data taken from [24] with permission from Dove Medical Press Ltd.

regularly have been, in recent years, replaced by long-acting compounds with higher potency and selectivity.

Ipratropium bromide (IB; Atrovent®) is a short-acting anticholinergic, causing bronchodilation by blocking muscarinic receptors in the airways and inhibiting the increase of cGMP intracellular levels [3].

Initially, IB was recommended as the therapy for stable COPD therapy alone or combined with short-acting β2 agonists such as salbutamol or fenoterol. They were effective in alleviating symptoms and improving lung function especially when given on a short-term basis.

The Lung Health Study (LHS) was the only randomized large scale study evaluating IB therapy in COPD patients with mild to moderate airflow obstruction. The primary end point was represented by the postbronchodilator FEV1 annual decline rate and respiratory and nonrespiratory morbidity and mortality over 5 years were evaluated secondarily [4]. Adherence was also considered as an outcome measure.

A total of 5887 participants were enrolled in three groups: one receiving usual care (UC), one receiving a smoking cessation intervention + IB (SI-A) and one receiving smoking cessation intervention + placebo (SI-P). Postbronchodilator FEV1 was found to be improved at 1 year as compared with baseline in both SI-A and SI-P groups and decreased significantly in UC group; subsequently it declined in all three groups but the lowest rate was in the SI-A group and was comparable with that of SI-P[4].

There were 149 (2.5%) deaths during the 5 year follow up were reported, most of them (60%) due to malignancies and 25% due to cardiovascular diseases. All cause mortality rate was the highest in SI-A, whereas in SI-P and UC they were comparable and, surprisingly, cardiovascular mortality rate was significantly higher in SI-A when compared with SI-P (0.92 vs 0.36%, p = 0.02); however, IB therapy could not be identified as a causation factor for these findings [4].

Hospitalizations were reported in 12.8% of study participants and cancer, cardiovascular diseases and nonmalignant respiratory tract disease led to hospitalization in 75% of these participants [4].

This study yielded very important conclusions once again supporting the effectiveness of smoking cessation intervention in reducing lung function decline in smokers with COPD.

Currently in COPD IB is rather recommended as a rescue ('acute') therapy to relieve bronchospasm in patients who do not tolerate

short-acting β2 agonists or as a second line inhaled maintenance bronchodilator when long-acting formulations are not available.

Long-acting anticholinergics

Tiotropium bromide (TTO; Spiriva®) is a long-acting anticholinergic drug with once-daily administration that selectively blocks M3 receptors in the airways [3]. It demonstrated a larger and more sustained therapeutic effect on lung function when compared with placebo and IB [5–9].

Several clinical studies lasting less than 1 year and having various comparators demonstrated that TTO was able to reduce dynamic hyperinflation, symptoms, rescue inhaler use, exacerbations and to improve health status.

Tiotropium: long-term efficacy

Two randomized studies performed in a total of 1456 COPD patients compared the safety and efficacy of TTO 18 µg once daily and placebo given for 1 year and the other two studies used as comparator ipratropium bromide 40 µg four times daily: tiotropium was found to significantly reduce exacerbations, improve health status, reduce dyspnea and rescue inhaler use; the therapeutic effect being superior to both placebo and IB [9,10].

In another study enrolling 1010 patients (n = 500 in tiotropium group and n = 510 in placebo) TTO therapy alone or added to inhaled/oral corticosteroids improved lung function significantly, and significantly reduced COPD exacerbation rate. This effect was more significant in patients with less severe COPD, in patients with more than three exacerbations during the previous year and in patients receiving inhaled corticosteroids during study period [11].

The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial was a 4-year multicenter randomized, double-blind, placebo-controlled parallel-group trial evaluating efficacy and safety of TTO 18 µg daily *de novo* or added to the usual COPD therapy (except for IB) in moderate-to-very severe stable COPD patients. The primary end point was represented by lung function (prerespectively postbronchodilator FEV1 decline rate), whereas secondary end points were safety, decline rates other lung function variables rates (forced vital capacity [FVC] or slow vital capacity), health status, COPD exacerbations and related hospitalizations. A total of 5993 patients were enrolled, 3006 in placebo and 2987 in TTO groups. Overall, TTO improved lung function (FEV1 and FVC) significantly when compared with placebo throughout the study period. Prebronchodilator FEV1 annual decline rate was similar in both TTO and placebo groups (30 ± 1 ml), whereas for postbronchodilator FEV1 it was higher in the placebo group (42 ± 1 ml versus 40 ± 1 ml in TTO). TTO reduced the prebronchodilator FVC decline rate as compared with placebo (39 ± 3 ml vs 43 ± 3 ml). A *post hoc* analysis identified a subset of patients not taking inhaled corticosteroids or long-acting β2 agonists at baseline in which TTO slowed significantly postbronchodilator FEV1 decline rate (40 ± 3 ml per year in tiotropium group versus 47 ± 3 ml per year in placebo group, $p = 0.046$). TTO significantly improved health status and significantly reduced exacerbations rate hazard ratios for exacerbations and for hospitalization for exacerbation being 0.86 for each event ($p < 0.001$ for exacerbations). TTO reduced significantly the mean number of exacerbations by 14% ($p < 0.001$) and the number of days of exacerbation per patient-year (12.11 vs 13.64 days, $p = 0.001$). In the intention to treat analysis a total of 941 all-cause mortality cases were reported, 14.9% in TTO group and 16.5% in placebo group (hazard ratio 0.89, $p = 0.09$). The adverse events most commonly reported were related to lower respiratory tract disorders such as COPD exacerbations, pneumonia and dyspnea [12,13].

The Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE study) was a 2-year multicenter, randomized, double-blind, double-dummy controlled trial assessing comparatively the effect of TTO 18 µg once daily and of fluticasone/salmeterol (500/50 µg twice daily) in the severe-to-very severe COPD population on the rate of health care utilization exacerbations, defined as COPD exacerbations, which required treatment with oral corticosteroids and/or antibiotics or required hospitalization. Secondary health status, postbronchodilator FEV1, all-cause mortality and study withdrawal rate were analyzed. More importantly, TTO improved health status and was associated with a comparable annual exacerbation rate when compared with slameterol/fluticasone (1.28 with salmeterol/fluticasone propionate group and 1.32 in the tiotropium group [rate ratio: 0.967; $p = 0.656$]). TTO was found to be associated with a higher withdrawal probability (29% greater than that of fluticasone/salmeterol, $p = 0.005$). The therapeutic effect on lung function was comparable for both study medications; however, that of TTO was more persistent [14].

When compared with salmeterol twice daily in a study enrolling 7376 patients with moderate-to-very severe COPD (3707 treated with tiotropium and 3669 treated with salmeterol), tiotropium significantly increased the time to the first exacerbation (187 vs 145 days), and the time to first severe exacerbation [15].

Tiotropium: long-term safety

An initial pooled analysis of tiotropium safety data from 4453 patients receiving TTO and 3384 patients receiving placebo identified lower risks of all cause mortality (relative risk 0.76), cardiovascular mortality (relative risk 0.57) and serious arrhythmias (relative risk 0.92) in patients receiving TTO. However, higher risks of tachycardia and other rhythm abnormalities were detected (relative risk 1.68 and 2.71, respectively) [16].

The UPLIFT study demonstrated that the TTO group had significantly ($p < 0.05$) lower relative risk of developing serious adverse events such as all types of cardiac events (0.84), congestive heart failure (0.59) and, myocardial infarction (0.71), as well as COPD exacerbations (0.84), dyspnea (0.61) and respiratory failure (0.69). Incidence of fatal events was 12.8% in the TTO group as compared with 13.7% in placebo group, hazard ratio 0.84 [12].

These results were in contrast with those of a meta-analysis carried out based on data from 14,783 patients. Significantly increased risk of cardiovascular death, myocardial infarction and stroke was identified to be associated with inhaled anticholinergics (overall relative risk of 1.58, $p < 0.001$, relative risk 1.73, $p < 0.001$ associated with ≥6 months' exposure). When safety analysis was restricted to TTO the relative risk was found to be even higher (relative risk 2.12, $p = 0.008$) [17]. However, its results were questioned and rebutted.

In the INSPIRE study a significantly higher incidence of pneumonia was found in salmeterol/fluticasone group as compared with TTO group, but in the latter the mortality rate was significantly higher (21 patients [3%] vs 38 patients [6%] in the tiotropium group, $p = 0.032$) [14]. However, mortality analysis was demonstrated to have many shortcomings in a subsequent paper [18].

More recently, TTO safety was again reviewed in a meta-analysis including data from 18,111 COPD patients: no significant difference in the incidence of adverse cardiovascular events was found in TTO patients (relative risk = 0.96) and of cardiovascular death (relative risk = 0.93), nonfatal myocardial infarction (relative risk = 0.84), and nonfatal stroke (relative risk = 1.04) in particular. The most interesting finding of this meta-analysis is the demonstration of smoking as a potential additive risk factor for cardiovascular adverse events: a smoking history of ≥55 pack-years was associated with a trend to a higher rate of cardiovascular adverse events in TTO patients [19].

Long-term bronchodilator inhaled therapy in COPD: long-acting β2 agonists

The main inhaled long-acting β2 agonists (LABAs) used in COPD therapy are represented by salmeterol and formoterol.

To date, LABAs are not commonly used as a first line long-acting bronchodilator therapy in milder COPD, as existing data suggest that their efficacy is enhanced by combining them with inhaled corticosteroids (ICST), the latter being recommended for COPD stages in which FEV1% pred is lower than 50%.

Both LABAs produce bronchodilation via a similar mechanism of action consisting of relaxation of smooth muscle cells in the airways after binding the β2 adrenoreceptor and increasing intracellular cAMP levels [20].

Both salmeterol and formoterol have β2-receptor affinity superior to that of their short-acting precursor salbutamol; formoterol exhibiting a higher receptor affinity when compared with salmeterol [20,21].

Long-acting β2 agonists have been shown to exert suppressing effects on neutrophilic inflammation by attenuating neutrophil adhesion, accumulation or activation and by increasing cell apoptosis [21]. Furthermore, formoterol has been also shown to interfere with production of cytokines such as IL-4,5,13, GM-CSF or INF-γ [22].

In terms of acute bronchodilator effect formoterol has been shown to have a faster onset of action and a more rapid maximal bronchodilator effect when compared with salmeterol (1 h as compared with 2 h), but the overall duration of effect was comparable for both compounds [22,23].

Short-term therapeutic effects (<1 year therapy) of salmeterol and formoterol in COPD have been evaluated in several studies having various end points of efficacy such as lung function, exercise capacity, exacerbation rate, health status, symptoms improvement or use of rescue bronchodilator; both salmeterol and formoterol demonstrated their short-term efficacy, especially on lung function, exacerbation rate, health status

or rescue inhaler usage whereas their therapeutic effects on exercise capacity and symptoms such as dyspnea remain unclear [24–26].

Data on LABAs long-term efficacy and safety in COPD rather come from larger scale studies in which they were evaluated along with ICST and placebo as comparators for LABA/ICST combinations.

Salmeterol: long-term efficacy

The most extensively evaluated LABA in COPD was salmeterol. In a placebo-controlled study enrolling 634 patients salmeterol 50 mg twice daily added to the regular therapy nonsignificantly reduced the rate of moderate and severe exacerbations in the intention-to-treat analysis, had a significant impact on overall exacerbations rate in per protocol analysis, rapidly reduced lung hyperinflation, maintained this effect over 12-month period and significantly improved health status [14].

Other studies assessed long-term efficacy and safety of salmeterol using it and inhaled corticosteroid fluticasone as active comparators for their combinations. The first such study was a randomized, placebo-controlled study assessing the efficacy and safety of 1-year therapy with salmeterol 50 µg twice daily, fluticasone 500 µg twice daily and salmeterol/fluticasone combination (Seretide Diskus, Advair Diskus 50/500 µg twice daily) and matching placebo in 1465 COPD patients. Salmeterol alone or in combination significantly improved pretreatment FEV, which was the primary end point as compared with placebo (treatment difference for salmeterol 73 ml, $p < 0.0001$ and for combination 133 ml, $p < 0.0001$). Improvements in health status, reduction of respiratory symptoms and rescue use of inhaled short-acting β2-agonist were also reported with all active treatments, the combination, however, demonstrating the most significant therapeutic effect [27].

Subsequently, a larger scale study, the Towards a Revolution in COPD Health (TORCH) study was conducted; this was a 3-year trial comparing again the same medications versus placebo in 6112 COPD patients with moderate-to-very severe COPD. The primary outcome was all causes of mortality and secondarily exacerbations rate, health status and lung function were assessed. Mortality rate was 13.5% in salmeterol group, 16% in fluticasone group, 15.2% in placebo group and 12.6% in combination group (absolute risk reduction combination vs placebo 2.6%, hazard ratio 0.825, 95% confidence interval 0.681-1.002; $p = 0.052$). COPD-related death rate was 6.1% for salmeterol comparable to that of placebo (6.0%) whereas for combination it was 4.7% (hazard ratio salmeterol vs placebo 1.01, 95% confidence interval [CI]; 0.88–1.53, $p = 0.30$; hazard ratio combination vs salmeterol 0.77, 95% CI 0.56–1.04, $p = 0.09$). Salmeterol both alone or combined with fluticasone reduced significantly the rate of hospitalizations for COPD exacerbations when compared with placebo (rate ratio combination therapy vs placebo 0.83, 95% CI 0.71–0.98, $p = 0.03$, rate ratio salmeterol vs placebo 0.82, 95% CI 0.69–0.96, $p = 0.02$).

Health status assessed with Saint George Respiratory Questionnaire (SGRQ) was significantly improved by in all treatment groups as compared with placebo but none of these improvements reached the clinical significance minimal threshold of 4 units of score(-3 for combination, -1.8 for fluticasone , -0.8 for salmeterol, +0.2 for placebo) [28].

The effects of salmeterol, fluticasone and their combination on lung function (FEV1) was also assessed in the TORCH study. Combination was the only intervention that produced an improvement in postbronchodilator FEV1 (+0.029 liters in combination vs -0.062 liters in placebo, difference of 0.092 [0.075-0.108], $p<0.001$), whereas salmeterol therapy was associated with a reduction in lung function loss when compared with placebo (-0.021 l in salmeterol versus -0.062 l in placebo, difference of 0.042 [0.025-0.058] $p<0.001$) [28]. When therapeutic effect on lung function decline annual rate was assessed this was found to be significant for components and combination when compared with placebo (FEV1 decline 55 ml/year with placebo, 42 ml/year with salmeterol and with fluticasone respectively, 39 ml/year with salmeterol/fluticasone, $p<0.001$ salmeterol/fluticasone versus placebo, $p = 0.003$ salmeterol versus placebo) [12]. In a subsequent analysis the efficacy and safety were analyzed according to baseline post-bronchodilator FEV1 (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage of severity). Salmeterol failed to show superiority to combination in all efficacy end points previously discussed and at all stages of COPD severity except for moderate/severe exacerbation annual rate in the very severe (stage IV) COPD, which was the lowest when compared with combination (1.4 vs 1.54), and to lung function decline rate in stage II (moderate COPD), which was the lowest (40 ml/year vs 44 ml/year for combinations). Salmeterol was associated with the highest all cause mortality rate and with a health

status deterioration in stage IV (24.6 vs 17.7% in combination group and 24.3% in placebo; increase of 0.4 in SGRQ score as compared with a decrease of -3.3 in combination and an increase of 2.6) [28]. Salmeterol/fluticasone combination also tended to reduce mortality risk in the same cohort [29].

Formoterol: long-term efficacy

Unlike salmeterol, which was assessed for long-term efficacy in COPD comparatively to placebo only, inhaled formoterol was evaluated when compared with budesonide their combination and placebo: in two 1-year studies performed in a pooled sample of 1834 COPD patients with study medications given as dry powder inhalation (DPI) formulations, both formoterol 9 µg, and its combination with budesonide 320 µg (Symbicort®, 320/9 µg) given twice daily decreased exacerbation rate improved lung function and health status as compared with placebo; however, the most significant therapeutic effects were produced by combined therapy [30,31].

Long-term efficacy of budesonide/formoterol combination formulated to be delivered via hydrofluoroalkane pressurized metered-dose inhaler (pMDI) at two different dosages (320/9 and 160/4.5 mg) and given twice daily were evaluated compared with formoterol DPI 9 µg twice daily and matching placebo in 1964 patients with moderate-to-very severe COPD. Both combination dosages were found to be superior to formoterol alone on 1 h post-dose FEV1, exacerbations rate, respiratory symptoms and health status, and higher combination dosage was also found to have larger therapeutic effect on pretreatment FEV1 [21].

Arformoterol is a racemic formoterol enantiomer that has been recently suggested to be a more potent bronchodilator than formoterol also having more prominent anti-inflammatory properties. It is currently used in the USA as an inhalation formulation for nebulization in COPD. A short-duration (12 weeks) placebo-controlled study performed in 345 patients with moderate-to-very severe COPD demonstrated that nebulized arformoterol 20 µg twice daily was comparable in therapeutic effect on lung function, health status and the rescue use of inhaled short acting β2 agonist to formoterol DPI 12 µg twice daily and both were significantly superior to placebo [32].

When nebulized arformoterol 50 µg daily was comparatively assessed with pMDI salmeterol 42 µg twice daily for 12 months both compounds demonstrated comparable efficacy on lung function, rescue use of inhalers, exacerbations rate and arformoterol improved to a greater extent the postbronchodilator FEV1 [33].

Indacaterol

Indacaterol (Onbrez®) is an ultralong-acting β2 agonist approved in Europe for COPD therapy. It was demonstrated to exert a bronchodilator effect with fast onset and lasting 24 h and consequently was recommended to be dosed once daily. The initial Phase II and III studies of shorter duration, performed with dosages of 150 or 300 µg demonstrated a sustained increase in lung function, a reduction of dyspnea severity and a significant improvement in health-related quality of life when compared with placebo or with other long-acting bronchodilators [33–35].

In a double-blind placebo-controlled 52-week study performed in patients with moderate-to-severe COPD, in which the efficacy and safety of indacaterol 300 µg (n = 437) or 600 µg (n = 428), once daily was compared with that of formoterol 12 µg twice daily (n = 435) and with that of placebo (n = 432). Indacaterol significantly improved the primary efficacy end point represented by the 24 h postdose FEV(1) by 170 ml (both doses) versus placebo and by 100 ml versus formoterol ($p < 0.001$) after 12 weeks and these significant differences persisted at 52 weeks. Compared to placebo, both bronchodilators significantly improved secondary efficacy end points such as dyspnea severity, daily symptoms or health-related quality of life. Indacaterol in particular, was superior to formoterol in its efficacy on dyspnea severity (measured with Transitional Dyspnea Index) and in reducing the rescue use of inhaled salbutamol. In terms of safety indacaterol exhibited a minimal cardiovascular effect [36].

Another study had an initial phase of 26 weeks in which patients with moderate-to-severe COPD were randomized to double-blind indacaterol 150 or 300 µg, placebo or open-label tiotropium 18 µg, all once daily. This was followed by an extension phase of 26 weeks during which patients completing the initial phase were allowed to continue indacaterol 150 or 300 µg once-daily or placebo for another period of 26 weeks. In the initial phase, the primary efficacy end point was trough FEV1 at 12 weeks whereas secondary end points included dyspnea, (Transitional Dyspnea Index [TDI]) health-related quality of life, exacerbations as well as safety end points such as serum potassium, blood glucose or QT interval corrected for heart rate

interval. A total of 1683 patients were enrolled and the increase in trough FEV1 at week 12 was 180 ml with both indacaterol doses versus placebo and 140 ml with tiotropium (all $p < 0.001$ vs placebo). Indacaterol also improved significantly dyspnea and quality of life compared with placebo, whereas tiotropium failed to cause such effects. Safety was found to be comparable among treatments [33]. A total of 415 subjects were enrolled in the extension phase which focused mainly on the long-term safety and secondarily on efficacy. Indacaterol was found to increase trough FEV1 and health-related quality of life, to reduce exacerbations rate and the use of salbutamol relative to placebo throughout the study [37].

However, data on the direct comparison of indacaterol with other long-acting bronchodilators would be very useful to further characterize the efficacy of this compound.

Long-term safety issues with LABA in COPD

In the TORCH study, safety was analyzed according to treatment allocation in the pooled initial analysis and also in the *post hoc* analysis according to treatment allocation and disease severity. In the initial analysis, 40% of patients in the salmeterol group (n = 1542) experienced a serious adverse event and in 20% the event caused study medication discontinuation as compared with 43 and 18% respectively in the combination group (n = 1546) [29]. In the *post hoc* analysis in the very severe COPD stage the incidences of serious adverse events were comparable in both salmeterol and combination groups, whereas the incidence of fatal adverse events was higher, although nonsignificantly, in salmeterol group (13%, n = 261) when compared with combination group (10%, n = 246; $p = 0.3589$) [29]. The incidence of serious and fatal adverse events increased with disease severity in all treatment groups and in placebo [28,29].

In the previous study assessing the long-term efficacy of salmeterol/fluticasone combination versus placebo and individual components, the incidences of overall treatment-related events was significantly higher for fluticasone when compared with salmeterol (19%/372 vs 12%/374, $p = 0.01$) and comparable with placebo for the latter [27].

In the study evaluating the effects of 1-year salmeterol therapy versus placebo, the incidence of adverse events serious, fatal or causing medication discontinuation did not differ significantly when compared with placebo [14].

In the case of formoterol both 1-year studies discussed previously, reported similar adverse events profiles among the study groups; however, in one of the studies the incidence of COPD-related adverse events was higher with formoterol than with combination, as was mortality rate, although no significant differences were reported [30]. In the other study, the highest incidence of adverse events was reported with placebo and the proportion of patients experiencing serious adverse events in formoterol group did not differ significantly from placebo or from combination groups [31].

When safety of formoterol (12 or 24 µg twice daily) was evaluated comparatively with that of slow-release theophylline and placebo it was found that, despite comparable efficacy on lung function, symptoms and rescue inhaler use, formoterol had a better safety profile when compared with theophylline [38].

Nebulized arformoterol and DPI formoterol long-term safety were evaluated comparatively in an open-label 52-week study following the initial 12 weeks of short-term placebo-controlled safety and efficacy studies. It was found that both formulations exhibited a similar safety profile [33].

Compared to inhaled salmeterol (pMDI) arformoterol 1-year therapy was associated with a higher incidence of tremor but the exacerbation rate and overall incidence of adverse events were comparable [33].

The overall safety of existing LABAs was appraised in several meta-analyses. Two of them regard particularly the COPD and both deriving data have to be interpreted with caution. The most recent meta-analysis included studies lasting at least 1 month, whereas the previous one focused on both asthma and COPD, and generally evaluated the broader β2-agonist class, including the short-acting compound salbutamol as well [39,40]. However, in COPD, on both short- and long-term basis, LABA therapy did not significantly increase the risk of respiratory deaths when compared with placebo (relative risk 1.09; 95% CI: 0.45–2.64) and combination with inhaled corticosteroids reduced the risk of respiratory deaths versus LABAs alone (relative risk 0.35; 95% CI: 0.14–0.93) [40].

In the study initially comparing indacaterol, tiotropium and placebo, followed by an extension for indacaterol and placebo, adverse events were reported to be mostly mild or moderate, and occurred in 76% patients receiving indacaterol 150 µg, 77% with indacaterol 300 µg and 68% of subjects receiving placebo, 300 µg and placebo. The incidence of serious adverse events

was 10.4, 12.3 and 10.5%, respectively. No significant effects of indacaterol on QT interval corrected for heart rate, serum potassium or serum glucose were reported [37].

A retrospective analysis on safety data in 4635 patients with moderate-to-severe COPD enrolled in studies lasting at least 6 months found that compared with placebo, indacaterol did not increase the risk of cardiovascular and cerebral adverse events, and that the associated relative risks were comparable in patients taking indacaterol with those taking other bronchodilators. Indacaterol was associated with a lower mortality risk when compared with placebo (relative risk 0.30, p = 0.054) [41].

Bronchodilator combinations in COPD

The existing data support the use of long-acting anticholinergics as a first-line maintenance bronchodilator therapy in milder COPD patients, whereas LABAs are rather effective when combined to ICST and given (better if added to bronchodilators, such as TTO) more advanced COPD. However, a combination of long-acting bronchodilators with different mechanisms of action would also be plausible and opportune.The existing short-term studies demonstrate that combination LABA + TTO might be more effective than the components; for example, formoterol-TTO combination was found to improve lung function, symptoms, health status and on a short-term basis reduce the use of rescue inhaler [15,42–45]. Data on the effects of long-term intervention with such a combination are not available yet but such studies are supported by short-term data.

Such combinations would be most suitable in milder COPD, and the possibility of once-daily dosing would represent an important advantage for maintaining an increased adherence to treatment.

A further advantage would be that such a combination could be given in the morning to those patients with daytime symptoms or in the evening for those with nighttime symptoms. In fact, this was already tested in a study performed over a period of 30 days and bronchodilator efficacy was found to be similar for both 'morning' and 'evening' approaches [43].

In severe and very severe COPD the addition of inhaled corticosteroids to the long-acting bronchodilator(s) is recommended as a maintenance regimen and in the case of LABAs this is supported by a large body of data, especially for long-term efficacy and safety. However, the effects of a triple combination TTO/LABA/ICST is less extensively evaluated. The Canadian Respiratory Clinical Research Consortium (CRCRC) study was a 1-year randomized double-blind, placebo-controlled trial assessing the effects of combination tiotropium (18 µg once daily) + fluticasone/salmeterol (250/25 µg two puffs twice daily), tiotropium (18 µg once daily) + salmeterol (25 µg, two puffs twice daily), and tiotropium alone (18 µg once daily), which failed to demonstrate any significant therapeutic benefit of the triple combination on overall exacerbations rate but documented the significant improvements in lung function and health status, and the significant reduction in COPD hospitalization rate. In the same study, TTO/salmeterol did not significantly improve lung function or hospitalization rate compared with placebo. However, these data have to be interpreted with caution as, according to the authors, more than 40% of patients who received tiotropium + salmeterol and tiotropium + placebo discontinued study therapy earlier and were subsequently given inhaled corticosteroids or long-acting β-agonists [46].

Conclusion

In stable COPD, inhaled bronchodilators are major components of the maintenance regimen, being required individually in moderate stages and combined or added to inhaled corticosteroids in more severe stages.

Currently, long-acting bronchodilators, whether β2-agonists or anticholinergics, are recommended for use, based on their demonstrated efficacy on lung function, respiratory symptoms or health status, whereas the use of short-acting formulations is rather considered for relieving acute symptoms ('rescue use') and, in the case of short-acting anticholinergics alone or combined with short-acting β2-agonists, as second options therapies when long-acting bronchodilators are not available or affordable.

The latter have the advantage of a more potent and long-lasting effect, which results in a reduction of the number of daily dosages and favor the adherence increase that is crucial for achieving an optimal control of the disease.

The Lung Health Study is the first study evaluating the long-term effects of an inhaled therapy and of smoking cessation on lung function decline, mortality and morbidity in COPD patients. Its results represented the basis for the subsequent shaping of the disease management guidelines, which were then adjusted based on clinical data from newer compounds.

Tiotropium bromide remains the long-acting bronchodilator of choice to be used as first line individual therapy in moderate stable COPD. Its long-term efficacy and safety are documented by several studies. The most recent one, the UPLIFT study, demonstrated that in COPD patients with milder disease, TTO might significantly reduce lung function decline and disease morbidity. Although some cardiovascular safety issues remain of concern and deserve further evaluation, owing to existence of additional risk factors such as smoking, the therapeutic benefit overcomes them on a both short- and long-term basis.

Data on long-term effects of the existing LABAs support their use in moderate COPD as a standalone or add on long-acting anticholinergic and in severe-to-very severe COPD as combination with inhaled corticosteroids. Such an approach resulted in a superior therapeutic effect on mortality, morbidity and lung function decline, such as those demonstrated in the TORCH study.

Despite the long-term efficacy and safety of inhaled long-acting bronchodilators being demonstrated in the existing studies, and despite these having contributed to a great deal to a more appropriate positioning of such therapies in the management of stable COPD, several pending issues, such as long-term effects of combined bronchodilators regimens and of bronchodilators/corticosteroids triple combinations on disease outcome, remain to be documented by the subsequent studies.

Future perspective

In COPD, long-term therapeutic interventions with various therapies are primarily aimed mainly at reducing lung function decline, improving health-related quality of life and reducing COPD related morbidity and mortality.

Of the existing therapeutic interventions, smoking cessation was the first demonstrated to be able to reduce the decline of lung function on a long-term basis, irrespective of the degree of lung impairment at the moment when it is applied.

Both the TORCH and UPLIFT studies subsequently demonstrated that LABAs/ICST combination and TTO exerted similar effects from qualitative points of view.

The major therapeutic benefit of inhaled bronchodilators is probably represented by reducing disease exacerbations and hospitalizations in particular. This was constantly demonstrated with all existing long-acting bronchodilators and should be used as a strong argument to motivate patients to use such compounds regularly.

However, there are other issues that need to be further evaluated, such as the long term effects of long-acting bronchodilator combinations, the place in stable COPD therapy of once-daily long-acting LABAs, the plausibility of treating COPD stage I and the long-term bronchodilator effects in nonsmoking COPD.

Combined treatment with long-acting bronchodilators that have different mechanisms of action is recommended by the existing guidelines in order to potentially increase the individual efficacy. This is even documented in studies with small samples and short duration for combinations such as TTO/formoterol; however, long-term effects of such an approach are not yet known.

Newer bronchodilating agents such indacaterol, a once-daily ultra LABA that has been assessed for its sustained bronchodilator potential in COPD and recently approved in some countries for this therapeutic indication. However, its impact on lung function decline is not as well known as the therapeutic potential of combining it with a long-acting anticholinergics.

Another issue that needs to be documented is whether the chronic bronchodilator therapy introduced according to current management guidelines is precocious enough to impact significantly on the natural history of the disease or if an earlier administration of such compounds would be of added benefit.

Chronic obstructive pulmonary disease is recognized as a chronic disease for which smoking is the most prominent risk factor. However, nonsmoking-related COPD is increasingly detected, especially as a consequence of indoor or outdoor noxious agents. In such a disease subset it is not known if exposure cessation would have an effect on lung function decline similar to smoking cessation, and if the long-term effects of the currently recommended therapies are comparable with those found in smoking-related COPD. None of the studies discussed in this review focused on this particular subset and hence, further studies are needed in order to better characterize the effectiveness of the existing therapies in this setting.

Finally, given that COPD is an inflammatory disease of the airways by definition and that from a certain point ahead, the local inflammation becomes systemic and impacts significantly on disease prognosis, the potential anti-inflammatory effects of inhaled therapies need to be further assessed. This has so far been evaluated with inhaled corticosteroids rather than with inhaled bronchodilators and as the latter pharmacological

class has also demonstrated various anti-inflammatory effects in preclinical studies, clinical studies with similar aims are necessary.

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Executive summary

- Chronic obstructive pulmonary disease is a chronic disease of the airways in which pharmacological therapy is aimed at improving symptoms, reducing exacerbation rate and improving quality of life.
- Long-acting bronchodilators such as tiotropium (anticholinergic), salmeterol, formoterol, (β2-agonists) are the therapeutic mainstay in moderate-to-very severe chronic obstructive pulmonary disease and their use is supported by the demonstrated long-term efficacy and by their good safety profiles.
- Large-scale studies, such as TORCH and UPLIFT, demonstrated that long-acting β2 agonists/inhaled corticosteroid combination and Tiotropium bromide exerted similar effects from qualitative points of view.
- The major therapeutic benefit of inhaled bronchodilators is represented by reduction of disease exacerbation rate and hospitalizations in particular.
- Such an effect should be used to motivate patients to adhere to the recommended therapeutic regime.
- Ultra long-acting β2 agonists such as indacaterol are the newcomers and more long-term data on their efficacy and safety are awaited.

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