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REVIEW

Role of indacaterol and the newer very long-acting β2-agonists in patients with stable COPD: a review

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Abstract: Bronchodilators are central drugs in the management of patients with chronic obstructive pulmonary disease (COPD). Indacaterol was the first agent of the novel family of very long-acting β2-agonists to be used as an inhaled bronchodilator for COPD and provides 24-hour therapeutic action, thus allowing once-daily administration. Data from clinical trials show that indacaterol has a bronchodilator effect similar to that of the anticholinergic tiotropium bromide and slightly higher efficacy compared with the long-acting β2-agonists, salmeterol and formoterol. Moreover, the safety profile is excellent and comparable with that of placebo. Concerning adherence with drug treatment and real-life management in respect to long-acting β2-agonists, once-daily dosing makes indacaterol more convenient for COPD patients and is likely to enhance patient adherence. Other very long-acting β2-agonists currently in development include vilanterol, olodaterol, and carmoterol, and these have shown good characteristics for clinical use in the studies reported thus far.

Keywords: chronic obstructive pulmonary disease, bronchodilators, very long-acting β2-agonists

Introduction

Inhaled bronchodilators have a central role in the treatment of chronic obstructive pulmonary disease (COPD) because they reduce respiratory symptoms, increase exercise tolerance, reduce the frequency of exacerbations, and improve quality of life. Bronchodilators include anticholinergic agents and β2-agonists, which are the currently recommended maintenance treatment for COPD.[1] Short-acting bronchodilators (salbutamol, ipratropium bromide) are the most effective drugs for rapidly improving respiratory symptoms as needed, while long-acting β2-agonists, such as salmeterol and formoterol, and the long-acting muscarinic antagonist, tiotropium bromide, are used in the treatment of stable disease.[2,3] Aclidinium bromide and glycopyrronium bromide were recently introduced as new long-acting muscarinic antagonists. The ability of β2-agonists to relax airway smooth muscle is due to their binding to the active site of β2-adrenoceptors on such muscle, which induces a signaling cascade resulting in muscle relaxation.[4] Based on the duration of this effect, long-acting β2-agonists need twice-daily administration. Indacaterol was introduced in 2009 as the first once-daily, long-acting β2-agonist approved in the European Union for maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD, to be administered at doses of 150 µg or 300 µg, and with the denomination of an ultra long-acting β2-agonist.[5] Drugs belonging to this new class may also be defined as very long-acting β2-agonists (VLABAs), and include indacaterol and a

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number of agents currently under development that provide sustained bronchodilation comparable with that of long-acting β2-agonists, allowing once-daily administration for patients with COPD.[6] Table 1 shows the main characteristics of the available bronchodilators. Adherence with long-acting β2-agonists in COPD patients is low, being estimated at 54%, so an effective once-daily β2-agonist would be a significant improvement in terms of adherence with bronchodilator therapy, reducing the morbidity and health care costs of the disease related to nonadherence.[7]

Here we review the evidence from randomized trials concerning the efficacy and safety of indacaterol with respect to placebo, the long-acting β2-agonists, and tiotropium, and summarize the characteristics of the VLABAs under current development.

Indacaterol: efficacy data

Placebo-controlled trials

The efficacy of indacaterol was shown by several trials in terms of improvement in lung function as well as clinical outcomes and quality of life. Most of these trials included patients with moderate or severe COPD, defined as a post-bronchodilator forced expiratory volume in one second (FEV_1) <80% and ≥30% of the predicted value and a post-bronchodilator FEV_1/forced vital capacity <70%. Spirometry-based end points included 24-hour post-dose FEV_1 (measured 24 hours after the previous dose) and other time points post dose (from 5 minutes to 24 hours); an increase in FEV_1 of 120 mL was considered to be the threshold for clinical relevance. Beyond lung function parameters, patient-orientated clinical end points were considered, ie, symptoms, dyspnea, exacerbation rates, use of rescue medication, days with no symptoms, and exercise tolerance. Evaluation of symptoms and health status was done using questionnaires like the St George's Respiratory Questionnaire (SGRQ), Transition Dyspnea Index (TDI), and the modified Medical Research Council scale.[8] The main data from the trials on indacaterol are reported in Table 2.

The first study was conducted with a trial design comprising two phases. The INHANCE (INdacaterol to Help Achieve New COPD treatment Excellence) study included a dose-finding stage with dose selection after 2 weeks of treatment, and a second stage evaluating efficacy and safety during 26 weeks of treatment.[9] In the dose-finding stage, patients were randomized into seven arms, ie, double-blind indacaterol 75, 150, 300, or 600 μg once daily, the long-acting β2-agonist formoterol 12 μg twice daily or placebo, or tiotropium 18 μg once daily. Selected doses of indacaterol (150 μg and 300 μg) were continued into the second stage for up to 26 weeks, while the other two indacaterol doses and formoterol were discontinued (see further on in this paper, in the discussion of indacaterol versus tiotropium).

As an extension to 6 months of the previous dose-finding INHANCE study, the INDORSE (INdacaterol DOse-finding extension on long teRm increaSe of FEV_1) study assessed the long-term efficacy of indacaterol 150 μg and 300 μg once daily versus placebo.[10] Concerning functional parameters, indacaterol increased the FEV_1 compared with placebo throughout the study, reaching the clinical threshold (difference of ≥170 mL at week 52). Indacaterol achieved significant reductions in COPD exacerbations and as-needed albuterol use. An improvement in health status (by SGRQ scores) was highlighted with active treatment.[10]

In the INLIGHT (INdacaterol efficacy evaLuation using 150 μg doses witH COPD paTients) study, Feldman et al evaluated the efficacy of indacaterol 150 μg once daily versus placebo in a large population of patients for 12 weeks.[11] Indacaterol significantly reduced the use of rescue medication and also the rate of days of poor control versus placebo. A significant difference in favor of indacaterol was found both at day 1 and after week 1; at week 12, the 24-hour post-dose FEV_1 was 130 mL higher than in the placebo group.

Table 1 Main characteristics of inhaled bronchodilators

Drug class	Onset of action	Duration of action	Administration
Short-acting β2-agonists	Rapid	Up to 6 hours	As rescue medication
Long-acting β2-agonists	Formoterol: rapid Salmeterol: slow	12 hours	Maintenance treatment TD
Very long-acting β2-agonists	Rapid	24 hours	Maintenance treatment OD
Short-acting muscarinic antagonists	Rapid	Up to 6 hours	As rescue medication
Long-acting muscarinic antagonists	Slow for tiotropium bromide and aclidinium bromide Rapid for glycopyrronium bromide	Aclidinium bromide 12 hours Tiotropium bromide 24 hours Glycopyrronium bromide 24 hours	Maintenance treatment TD Maintenance treatment OD Maintenance treatment OD

Abbreviations: TD, twice daily; OD, once daily.

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Table 2 Details of trials on indacaterol

Trial	Patients, n (completed)	Duration	Design	Indacaterol	Control group	Outcomes
INDORSE[10]	414 (336)	52 weeks	Core: randomized, double-blind indacaterol or placebo, open-label tiotropium (26 weeks) Extension: subjects previously randomized to indacaterol or placebo continued double-blind treatment (26 weeks)	150 μg OD 300 μg OD	Placebo	24-hour FEV_1 at 52 weeks, exacerbations, SGRQ
INABLE[12]	90 (74)	21 days	Randomized, double-blind, placebo-controlled, two-period crossover	300 μg OD	Placebo	Exercise endurance time at week 3, IC, 75 minutes post dose FEV_1 and FVC
INLIGHT 1[11]	416 (364)	12 weeks	Double-blind, parallel-group	150 μg OD	Placebo	24-hour FEV_1 at week 12, use rescue medication, percentage of days of poor control
INSIST[14]	1,123 (1,034)	12 weeks	Randomized, parallel-group	150 μg OD	Salmeterol 50 μg TD	FEV_1 standardized area under curve from 5 minutes to 11 hours and 45 minutes and 24-hour FEV_1 at week 12, TDI, use of rescue medication
INLIGHT 2[13]	1,002 (838)	26 weeks	Randomized, double-blind	150 μg OD	Salmeterol 50 μg TD	24-hour FEV_1 at week 12, SGRQ, dyspnea
INTEGRAL[15]	68 (61)	14 days	14-day block crossover. Randomized, double-blind indacaterol or placebo, open-label salmeterol	300 μg OD	Placebo Salmeterol 5 μg TD	24-hour FEV_1 at day 14
INVOLVE[16]	1,732 (1,282)	52 weeks	Randomized, double-blind double-dummy	300 μg OD 600 μg OD	Placebo Formoterol 12 μg TD	24-hour FEV_1 at week 12, TDI, use of rescue medication, SGRQ, exacerbations, symptoms on diary cards
INTIME[17]	169 (153)	14 days	14-days incomplete block (three of the four treatments) crossover	150 μg OD 300 μg OD	Placebo Tiotropium 18 μg OD	24-hour FEV_1 at day 14
INHANCE[18]	1,683 (1,291)	26 weeks	Double-blind indacaterol or placebo, open-label tiotropium	150 μg OD 300 μg OD	Placebo Tiotropium 18 μg OD	24-hour FEV_1 at week 12, TDI, SGRQ, exacerbations
INTENSITY[19]	1,593 (1,477)	12 weeks	Randomized, parallel-group, blinded, double-dummy	150 μg OD	Tiotropium 18 μg OD	24-hour FEV_1 at week 12, TDI, SGRQ, use of rescue medications, days with no symptoms

Abbreviations: INDORSE, INdacaterol DOse-finding extension on long teRm increaSe of FEV_1 study; INABLE, INdacaterol: endurAnce, exercise-Based, and Lung Evaluation study; INLIGHT, INdacaterol efficacy evaLuation using 150 μg doses witH COPD paTients studies; INTEGRAL, INdacaterol: Twenty four hours Efficacy duration using salmeterol study; INVOLVE, Indacaterol value in COPD longer term Validation of Efficacy and safety study; INTIME, INdacaterol and TIotropium: Measuring Efficacy study; INHANCE, INdacaterol to Help Achieve New COPD treatment Excellence study; INTENSITY, INdacaterol Towards Establishment of cliNical SuperiorITY study; IC, inspiratory capacity; TD, twice daily; OD, once daily; SGRQ, Saint George Respiratory Questionnaire; TDI, Transition Dyspnea Index; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second.

Inspiratory capacity, which is an index of end expiratory lung volume, was investigated during exercise and at rest in the INABLE (INdacaterol: endurAnce, exercise-Based, and Lung Evaluation) study. Inspiratory capacity is a valid indirect indicator of functional residual capacity and thus of the degree of lung hyperinflation. In patients treated with indacaterol 300 μg once daily, inspiratory capacity was significantly improved versus placebo, with regard to both the resting value and the increased end-exercise value after 3 weeks, indicating a reduction in lung hyperinflation.[12] Exercise endurance time was longer with indacaterol than with placebo after the first dose and after 3 weeks.

Trials versus twice-daily, long-acting β2-agonists

Several studies have compared the efficacy and safety of indacaterol against the twice-daily, long-acting β2-agonists, salmeterol and formoterol, in patients with moderate-to-severe COPD defined according to international COPD guidelines. The primary end point of these studies was

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24-hour post-dose FEV_1; other patient-related outcomes considered were breathlessness, as-needed use of short-acting bronchodilators, exacerbations, and health status. The efficacy of once-daily indacaterol 150 µg versus twice-daily salmeterol 50 µg was investigated in the INLIGHT-2 (Indacaterol efficacy evaluation using 150 µg doses with COPD patients), and INSIST (INdacaterol: investigating SuperiorIty versus SalmeTerol) studies.[13,14] The 24-hour post-dose FEV_1 after 12 weeks in the indacaterol group was 170 mL higher than in the placebo group and 60 mL higher than in the salmeterol group, and remained higher at week 26. Patients receiving indacaterol used less rescue medication and had a greater percentage of days with no rescue use. Active treatments (both indacaterol and salmeterol) improved the TDI and health status as assessed by SGRQ compared with placebo, with differences between the two active treatments favoring indacaterol.

In the INTEGRAL (INdacaterol: Twenty four hours Efficacy duration using salmeterol) study, patients were randomized to receive indacaterol 300 µg once daily, salmeterol 50 µg twice daily, or placebo daily. FEV_1 on day 14 (the primary end point) was 200 mL higher than in the placebo group and 90 mL higher than in the salmeterol group. FEV_1 was also assessed at different time points on days 1 and 14; indacaterol was significantly more effective than placebo at all time points, and showed a significantly higher FEV_1 compared with salmeterol at many post-baseline time points, including 5 minutes post dose.[15]

Comparison with formoterol also resulted in a favorable profile for functional and clinical end points. Dahl et al compared the efficacy and safety of indacaterol 300 µg and 600 µg with that of the twice-daily, long-acting β2-agonist formoterol 12 µg over one year in patients with moderate-to-severe COPD in the INVOLVE (Indacaterol value in COPD longer term Validation of Efficacy and safety) study.[16] The primary efficacy variable was FEV_1 measured 24 hours post dose after 12 weeks. The 24-hour post-dose FEV_1 at week 12 significantly increased on indacaterol (both doses) versus both placebo and formoterol, maintaining a significant difference at the 52-week evaluation. All symptomatic outcomes improved with both active treatments compared with placebo. Both drugs significantly reduced the risk compared with placebo when the time to first COPD exacerbation was evaluated.

Trials versus tiotropium

The long-acting anticholinergic tiotropium bromide was also compared with indacaterol. The first controlled trial that compared the bronchodilation obtained with indacaterol and tiotropium was INTIME (INdacaterol and TIotropium: Measuring Efficacy). Patients received indacaterol 150 µg or 300 µg, tiotropium 18 µg, and placebo each for 14 days, separated by a 14-day washout between each treatment period. Both treatments were significantly more effective than placebo. Once-daily indacaterol at doses of 150 µg and 300 µg was at least as effective as tiotropium, but had a faster onset of action (within 5 minutes) on the first day of dosing.[17] Two other trials including larger populations of patients were conducted, ie, the INHANCE study that, in the second stage, compared the efficacy of indacaterol (150 µg and 300 µg) with placebo and tiotropium over 12 weeks of treatment, and the INTENSITY (INdacaterol Towards Establishment of cliNical SuperiorITY) study, which demonstrated the noninferiority of indacaterol 150 µg once daily versus tiotropium using FEV_1 values, but also symptom assessment by the TDI and SGRQ, and use of rescue medication.[18,19] Regarding functional end points, both treatments were effective against placebo; in the INHANCE trial, after week 12 in patients receiving indacaterol, the 24-hour post-dose FEV_1 increased versus placebo by 180 mL (with indacaterol doses of 150 µg and 300 µg) and in patients receiving tiotropium by 140 mL versus placebo, thereby achieving the threshold for clinical relevance in both treatment groups. In the second trial, absolute FEV_1 values were 1.44 L with indacaterol and 1.43 L with tiotropium at week 12, such a difference being comparable. The mean TDI score significantly increased compared with placebo at all time points with both active treatments, and there was also a significant difference between indacaterol 300 µg and tiotropium at weeks 4, 8, and 12. Indacaterol-treated patients used less rescue albuterol than tiotropium-treated patients and had a higher proportion of days without any rescue use and of nights without awakenings. In both trials, the incidence of adverse events was similar across treatments.

Indacaterol: safety and tolerability data

Inhaled β2-agonists can have systemic effects due to their bioavailability; such effects, mediated by stimulation of β2-adrenergic receptors, are particularly important in the cardiovascular system and include tachycardia, increased blood pressure, a prolonged QT interval, hyperglycemia, hypokalemia, and muscle tremors. It must be considered that many patients with COPD are elderly and often have several comorbidities, so it is particularly important to evaluate the safety of maintenance bronchodilator treatment.

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The safety and tolerability of indacaterol was evaluated in all the relevant clinical trials, so could be assessed in a large population of patients with COPD at the approved doses of 150 µg and 300 µg (in the US, only the 75 mg dose is approved by the US Food and Drug Administration) and also at the higher dose (not approved for clinical use) of 600 µg daily for up to one year without observation of significant issues.

Data from clinical studies of 12–52 weeks' duration in patients with moderate-to-severe COPD receiving double-blind indacaterol at doses of 75 µg (449 patients), 150 µg (2,611 patients), 300 µg (1,157 patients), and 600 µg (547 patients) once daily compared with formoterol 12 µg twice daily (556 patients), salmeterol 50 µg twice daily (895 patients), tiotropium 18 µg once daily (1,214 patients), or placebo (2,012 patients) were screened.[20] The incidence of adverse events was similar in the indacaterol and placebo groups and, in most cases, reflected the typical signs and symptoms of COPD itself. Also, the risk of a "serious adverse event" (fatal or life-threatening, resulting in persistent or significant disability/incapacity, constituting a congenital anomaly/birth defect, requiring inpatient hospitalization or prolongation of existing hospitalization, or medically significant), including acute respiratory events, was similar in all indacaterol groups compared with placebo. Systemic β2-adrenoceptor-mediated effects (on QTc interval, plasma potassium, and blood glucose) were rare and showed no clinically significant changes with indacaterol treatment.

Cough, usually mild and transient, was frequently reported in the trials, a few minutes after inhalation, by up to 20% of patients.[11,14,15,18] In the study by Feldman et al, worsening of COPD and cough were the most frequent adverse effects; the onset of cough following inhalation was predominantly within 15 seconds of inhalation and was not associated with bronchospasm or any increase in study discontinuation rates.[11] Cough occurred at a higher frequency in the indacaterol groups compared with placebo (2.9%–12.4% versus 0.9%) in a dose-ranging trial; however, the incidence decreased over the course of the study, and the incidence on indacaterol was similar to that on placebo after 7 days.[21]

Indacaterol has a good cardiovascular safety profile in patients with COPD. β2-agonists, like other adrenergic compounds, can prolong the QT interval. In one randomized, double-blind, parallel-group, placebo-controlled, and positive-controlled study in healthy subjects, 404 individuals were randomized to receive indacaterol (at doses of 150, 300 or 600 µg), placebo, or placebo/moxifloxacin.[22] The primary endpoint was the change in QTcF (QT interval corrected for heart rate using Fridericia's formula) from baseline on day 14. In this study, indacaterol did not show any clinically relevant effect on the QT interval, with maximal time-matched mean treatment differences from placebo in QTcF change from baseline on day 14 of 2.66, 2.98, and 3.34 msec for indacaterol 150 µg, 300 µg, and 600 µg, respectively.

Analysis of clinical trials including 4,635 patients with moderate-to-severe COPD who were enrolled into studies of at least 6 months' duration and treated with indacaterol, placebo, or other bronchodilators (formoterol, salmeterol, tiotropium) showed that the cardiovascular and cerebrovascular safety profiles were similar to those for placebo and comparable with those for other long-acting β2-agonists.[23] Moreover, the safety of a single supratherapeutic dose of indacaterol was also investigated.[24] Single doses of indacaterol 400, 1,000, 2,000, and 3,000 µg were given to patients with moderate or severe COPD, with minimal systemic effects and no clinically significant electrocardiographic changes.

Issue of adherence

Adherence with treatment is certainly a major problem in patients with chronic disease, and less than 50% of patients receiving drug therapy follow it according to the physician's directions.[25] In the treatment of COPD, once-daily administration is particularly attractive for patient drug compliance.[26] In COPD, as for other chronic diseases, poor compliance is common and associated with increased rates of morbidity, health care expenditure, diminished quality of life, hospitalizations, and mortality.[27]

Incorvaia et al evaluated changes in adherence with drug treatment in patients with COPD receiving a structured educational program.[28] The study included 100 patients who were prescribed drug treatment by their primary care physician according to the updated version of the guidelines on COPD.[1] At the first visit, 34% of patients had stopped one or more of the prescribed drugs without their physician's authorization, and 53% did not use the correct dosage, giving an adherence rate of 47%. After the educational program, when patients attended the maintenance rehabilitation course 6 months later, the adherence rate had increased to 87.4%. This shows that patient education can greatly improve adherence with prescribed drugs in patients with COPD. When the study was performed, indacaterol was not commercially available, so the adherence evaluation concerned long-acting β2-agonists, inhaled corticosteroids, given singly or in combination, and tiotropium. Once-daily dosing of indacaterol is more convenient for patients and is likely to represent a compliance-enhancing advantage. Randomized

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studies of the effects of patient education on adherence are warranted to improve further the role of indacaterol in COPD treatment.[29]

VLABAs in development

Vilanterol

Vilanterol trifenatate has shown high potency, selectivity, rapid onset, a long duration of action in vitro, and low oral bioavailability. Higher selectivity for the β2-adrenoreceptor than salbutamol, formoterol, and indacaterol was detected.[30] Table 3 reports the main data from the trials available on vilanterol thus far. A placebo-controlled trial in patients randomized to receive five doses of vilanterol (3, 6.25, 12.5, 25, or 50 μg) or placebo once daily for 28 days found that the once-daily doses of 25 μg and 50 μg provided both statistically and clinically relevant 24-hour improvements in lung function compared with placebo. All doses of vilanterol had a safety and tolerability profile similar to that of placebo.[31] The safety of vilanterol was confirmed in a trial evaluating the drug alone (at the dose of 50 μg) or in combination with umeclidinium, a long-acting muscarinic antagonist, at a dose of 500 μg. Coadministration of single inhaled doses of umeclidinium and vilanterol to healthy subjects was well tolerated and not associated with meaningful changes in systemic exposure or pharmacodynamic effects compared with administration of either compound individually.[32] Further, studies were performed on the association of vilanterol with an inhaled corticosteroid. In one trial in patients with moderate-to-severe COPD, fluticasone furoate/vilanterol 100/25 μg provided rapid and significant sustained bronchodilation at 24 weeks; improvement in lung function to a similar extent was found with fluticasone furoate/vilanterol 50/25 μg and to a somewhat lesser extent with vilanterol 25 μg alone.[33] In another trial, fluticasone furoate/vilanterol provided rapid and significant sustained improvement in FEV_1 in patients with moderate-to-severe COPD, which was not influenced by the dose of fluticasone furoate.[34]

Olodaterol

Olodaterol was pharmacologically characterized in preclinical models in 2010.[35] To evaluate the mechanisms behind its long duration of action, different aspects of olodaterol

Table 3 Details of trials on vilanterol

Study	Patients (n)	Duration	Design	Interventions	Outcomes	Results
Hanania et al[31]	605	28 days	Randomized, double-blind study	Vilanterol 3 μg 6.25 μg 12.5 μg 25 μg 50 μg Placebo	24-hour FEV_1 at day 28, use of rescue medications	Vilanterol showed a significant, dose-dependent, improvement in trough FEV_1 compared with placebo
Kelleher et al[32]	16	Single inhaled dose	Single-center, double-blind, placebo-controlled, four-way, randomized, crossover trial	Vilanterol 50 μg Umeclidinium 500 μg Placebo	Safety Pharmacodynamic and pharmacokinetic analysis	Study treatments were safe and well tolerated and no serious adverse events or deaths were reported
Kerwin et al[33]	1,030	24 weeks	Multicenter, randomized, placebo-controlled, double-blind, parallel-group study	FF/vilanterol 100/25 μg 50/25 μg Vilanterol 25 μg FF 100 μg Placebo	Weighted mean FEV_1 (0–4 hours post dose on day 168) Trough FEV_1* (23–24 hours post dose on day 169) Adverse events	The combination FF/vilanterol significantly improved FEV_1 versus placebo No significant difference was seen between FF/VI 100/25 μg and VI 25 μg for trough FEV_1
Martinez et al[34]	1,224	24 weeks	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study	FF/vilanterol 200/25 μg 100/25 μg Vilanterol 25 μg FF 200 μg FF 110 μg Placebo	Weighted mean FEV_1 (0–4 hours post dose on day 168) trough FEV_1* (23–24 hours post dose on day 169) Adverse events	Significant increase in weighted mean FEV_1 and trough FEV_1 for FF/vilanterol 200/25 μg and 100/25 μg versus placebo. The difference between FF/vilanterol 200/25 μg and vilanterol 25 μg in change from baseline trough FEV_1 was not statistically significant

Note: *Trough FEV_1: mean volume of air that can be forced out in one second after taking a deep breath approximately 24 hours after the last administration of study drug.
Abbreviations: FF, fluticasone furoate; FEV_1, forced expiratory volume in one second; VI, vilanterol.

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were analyzed, including its lipophilicity and propensity to accumulate in the lipid bilayer, as well as its tight binding to the β2-receptor. According to its physicochemical properties, olodaterol showed a moderate association with lipid bilayers, while kinetic as well as equilibrium binding studies indicated the presence of a stable [(3)H]olodaterol/β(2)-AR complex with a dissociation half-life of 17.8 hours due to ternary complex formation.[36]

A double-blind, placebo-controlled, crossover study in 36 COPD patients including 24-hour spirometry, safety, tolerability, and pharmacokinetics (in a subset of patients) evaluated the effect of five doses of olodaterol (2, 5, 10, and 20 μg; 40 μg in an open label extension phase). The mean baseline prebronchodilator FEV_1 was 1.01 L (37% of predicted). All doses of olodaterol gave significantly greater bronchodilation compared with placebo in 24-hour FEV_1 post dose ($P < 0.001$); a clear dose-response relationship was observed, with values ranging from 0.070 L for olodaterol 2 μg to 0.119 L for olodaterol 20 μg. Pharmacokinetic evaluation of peak plasma concentrations and renal excretion suggested no obvious deviation from dose proportionality over the dose range investigated. All treatments were well tolerated.[37]

Carmoterol

Carmoterol is a non-catechol β2-adrenoceptor agonist with structural elements from formoterol and procaterol. Carmoterol has a 53 times higher affinity for β2-adrenoceptors than for β1-adrenoceptors, mainly because of the methoxyphenyl group in the seventh transmembrane region.[38] Its onset of action is rapid and prolonged, as showed by in vitro and in vivo studies. In particular, carmoterol demonstrated rapid activity in vitro comparable with that of formoterol and a longer duration of muscle relaxation than formoterol and salmeterol.[39,40] Phase II studies investigated the safety and tolerability of carmoterol administered in multiple escalating doses to patients with COPD, with no significant dose-effect response concerning blood parameters or cardiovascular events.[41] Controlled studies of its clinical efficacy are not yet available.

Conclusion

Bronchodilators are of central importance in the symptomatic management of COPD. Indacaterol was the first VLABA to be introduced, the 24-hour activity of which allows once-daily administration. This agent is now approved by the European Medicine Agency for the treatment of COPD. The available evidence shows that indacaterol provides efficacy comparable with, if not superior to, the other current bronchodilators used as maintenance treatment in terms of improving lung function and quality of life. Importantly, indacaterol is as rapidly effective as short-acting β2-agonists on the first day of use,[42] and this favors patient recognition of efficacy. Moreover, data from clinical trials indicate an excellent safety and tolerability profile, with a rate of adverse effects comparable with that of placebo; this includes cardiovascular effects, which are particularly important for β2-agonists. Available data indicate similar efficacy and safety for other VLABAs, such as vilanterol (including in fixed combination with the inhaled corticosteroid fluticasone furoate and the long-acting muscarinic antagonist umeclidinium) and olodaterol. Compared with twice-daily, long-acting β2-agonists, once-daily dosing of a VLABA appears to be more convenient for COPD patients and is likely to enhance their long-term adherence with treatment, which is a critical issue in the management of chronic diseases like COPD. On the other hand, the potential risks inherent with long-acting β2-agonists, especially when patients with COPD plus asthma (who need a treatment based on inhaled corticosteroids) are treated only by VLABAs must not be overlooked.

Disclosure

The authors report no conflicts of interest in this work.

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