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CLINICAL REVIEW

Efficacy of indacaterol in the treatment of patients with COPD

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Abstract

Effective bronchodilation is an important part of the management of patients with chronic obstructive pulmonary disease (COPD) and can improve breathlessness and ability to undertake physical activities. Indacaterol is a new once-daily, long-acting inhaled bronchodilator for COPD. We review here the efficacy of indacaterol as a bronchodilator, including its impact upon symptoms and health status. The evidence reviewed comprises four placebo-controlled clinical studies of indacaterol treatment, three of which included treatment arms with one of the other long-acting inhaled bronchodilators (once-daily tiotropium or twice-daily salmeterol or formoterol), in 4,833 patients with moderate-to-severe COPD. Indacaterol had a bronchodilator effect significantly greater than formoterol and salmeterol, and similar to tiotropium. Its effect on symptoms and health status was similar or significantly greater than the other bronchodilators. The safety profile was similar to placebo. Once-daily indacaterol is an effective and beneficial maintenance bronchodilator treatment for patients with moderate-to-severe COPD.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) generally present with symptoms of breathlessness on exertion, chronic cough, wheeze, sputum production and chest tightness. COPD is also characterised by airflow obstruction, the presence of which should be confirmed by spirometry. As the disease progresses, breathlessness limits patients' activities, and health status (or health-related quality of life) starts to deteriorate. However, the symptoms and impaired health status that characterise COPD can respond to pharmacological therapies.[1]

Long-acting inhaled bronchodilators are the most effective pharmacological agents for reducing COPD symptoms and their impact. These drugs have an important role in the management of COPD in patients who are still symptomatic despite treatment with a short-acting inhaled bronchodilator such as ipratropium or salbutamol.[1,2] They have been shown to improve symptoms, exercise capacity and health status, and to decrease the frequency of exacerbations.[3–5] Changes in these patient-centred outcomes are considered to be at least as important as (or even more important than) changes in lung function in the overall management of COPD.[6]

Four inhaled long-acting bronchodilators are available, taken either once or twice daily. The efficacy and safety of the twice-daily agents (the β_2-agonists, salmeterol and formoterol) have been demonstrated when given as monotherapy and in fixed-dose combination with inhaled corticosteroids (ICS).[5,7] The once-daily anticholinergic bronchodilator tiotropium has been available for several years and has an established efficacy and safety profile.[3,4,8,9] A once-daily β_2-agonist bronchodilator, indacaterol, was introduced in 2009.[10] The four clinical studies discussed here[11–14] provide a large-scale and comprehensive evaluation of the efficacy and safety of indacaterol and include comparisons with the available long-acting inhaled bronchodilators. The objective of this paper is to review the efficacy of this new once-daily bronchodilator with respect to these published clinical studies and to discuss its use in the treatment of COPD.

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Table 1. Details of the four studies reviewed

Study no.	Ref.	Design	Duration	Treatments	No. of pts randomised
STUDY 1 NCT00624286	11	Randomised, double-blind placebo-controlled	12 weeks	Indacaterol 150 µg od Placebo	416
STUDY 2 NCT00463567	12	Randomised, double-blind placebo-controlled	6 months	Indacaterol 150 µg od Indacaterol 300 µg od Tiotropium 18 µg od (open label) Placebo (to indacaterol)	1,683
STUDY 3 NCT00567996	13	Randomised, double-blind placebo-controlled	6 months	Indacaterol 150 µg od Salmeterol 50 µg bid Placebo	1,002
STUDY 4 NCT00393458	14	Randomised, double-blind placebo-controlled	1 year	Indacaterol 300 µg od Indacaterol 600 µg od Formoterol 12 µg bid Placebo	1,732

od = once-daily; bid = twice daily

Evidence reviewed

We reviewed the clinical evidence from four studies.[11–14] All were randomised and double blind with respect to placebo. They also compared the two twice-daily bronchodilators salmeterol (Study 3) and formoterol (Study 4), both given double blind. Another study included tiotropium given open-label (Study 2). The designs of the four studies are summarised in Table 1.

Patients

The patients enrolled in the studies had a clinical diagnosis of moderate-to-severe COPD, defined according to the level of airflow obstruction set out in the international COPD guidelines current at the time of designing the studies:[15] forced expiratory volume in one second (FEV_1) between 30% and 80% of predicted normal value and an FEV_1/forced vital capacity (FVC) ratio of less than 0.7 (both measured after four puffs of salbutamol). Patients were aged 40 years or over, with a smoking history of at least 20 pack-years. A majority (51–57%) of patients had moderate airflow limitation and were in GOLD stage II. Most of the rest (39–43%) had severe disease (GOLD stage III), and a small proportion had either mild (GOLD I; <4%) or very severe (GOLD IV; <3%) disease. The patients were not enrolled if they had had a recent chest infection or had been hospitalised for an exacerbation or respiratory infection in the six weeks before screening. Patients with a history of asthma were excluded.

Patients with clinically significant conditions that might have compromised their safety or interfered with the study measurements were excluded. Such conditions included unstable ischaemic heart disease, arrhythmia (patients with stable atrial fibrillation were permitted to enter the studies), uncontrolled hypertension, hypokalaemia, and diabetes type I or uncontrolled diabetes type II. Patients taking certain drugs were excluded in order to recruit a population of COPD patients in whom treatment effects (including safety) could be consistently measured. These included non-potassium-sparing diuretics, non-selective β-blockers, and drugs that might significantly prolong the QTc interval on ECG.

Measurements

a) Spirometry (FEV_1)

The primary endpoint of all the studies was FEV_1 at its 'trough' effect (i.e. 24 hours after the previous morning's dose) after 12 weeks of treatment. The 12-week time point was chosen since this is the minimum period required to demonstrate efficacy on FEV_1 for the purposes of formal drug registration, and to minimise the impact of patient dropout during the later stages of the longer-term studies. Results for other endpoints are presented here for the same time point.

A difference between indacaterol and placebo of 120 mL in their effect on trough FEV_1 was pre-specified as clinically relevant. This is the mid-point of the 100–140 mL range considered as clinically relevant compared with placebo.[6] A positive effect on trough FEV_1 reflects bronchodilator benefit in the early morning, before taking that day's treatment, which is a difficult time of day for COPD patients.[16,17]

FEV_1 was also measured in the first few minutes after the first dose, as a measure of onset of action. A fast onset may be beneficial in giving patients confidence that they have taken their medication correctly, and may help their adherence to treatment.[18]

b) Breathlessness

Breathing difficulties are the most common reason for COPD patients to seek medical attention.[19] Breathlessness, or dyspnoea, is the most troubling and distressing symptom for COPD patients,[20,21] limiting a patient's ability to undertake exercise or even everyday activities. Such limitations can impair a patient's health status. Bronchodilators can reduce breathlessness both as a direct effect of dilating the airways and by allowing more

efficient lung emptying on expiration, thus reducing the air trapping (or hyperinflation) that is characteristic of COPD.

Breathlessness was measured using a validated clinical rating in three of the studies with indacaterol (Studies 2, 3 and 4). The transition dyspnoea index (TDI) is administered by a trained assessor and measures the patient's functional impairment due to breathlessness in three areas: the ability to carry out usual activities; the magnitude of the task that causes breathlessness; and the magnitude of the effort required to cause the breathlessness. It measures the change in severity of breathlessness from baseline[22] using a seven-point scale from –3 (major deterioration) to +3 (major improvement). A change of 1 point is considered to be the minimal clinically important difference (MCID).[23,24] In the indacaterol studies, TDI results were presented as the mean score and in terms of the proportion of patients achieving the 1-point threshold for the MCID.

c) Use of as-needed salbutamol

During the studies, the patients were given salbutamol to use as-needed to relieve breathlessness ('rescue' use). They recorded the daily amount of salbutamol used in this way. The use of salbutamol reflects the severity and/or frequency of COPD symptoms experienced by the patients,[16] and is therefore an indirect measure of how well the study treatments controlled these symptoms.

d) Exacerbations

Exacerbations are defined as an acute worsening of symptoms, beyond normal day-to-day variation, that is sustained over several days. Exacerbations are among the commonest causes of hospital admission and death amongst patients with COPD, and they are associated with increased loss of lung function[25] and faster deterioration of health status.[26] Reducing the severity and frequency of exacerbations is one of the main objectives of COPD management.[6] The frequency of exacerbations is generally related to disease severity, and a history of frequent exacerbations (two or more per year) is the major predictor of whether a patient will continue to exacerbate frequently.[27] In the indacaterol studies, COPD exacerbations were defined as the onset or worsening of more than one symptom (i.e. dyspnoea, cough, sputum purulence or volume, or wheeze) for more than three consecutive days, with documented additional treatment or emergency or hospital admission.

The studies with indacaterol were designed to evaluate its efficacy against a background of stable disease, so patients were not required to have a history of frequent exacerbations.

e) Health status

COPD symptoms arise not only through airflow limitation but also through other elements of the disease – such as fatigue and muscle weakness, impaired sleep, and altered mood – which all contribute to the impact of the disease upon the patient. These different aspects can be captured by measuring health status (also known as 'health-related quality of life'). Such questionnaires cover the physical, emotional and psychological effects of COPD, particularly the practical aspects of disturbance to daily life. The most widely used questionnaire in COPD studies of pharmacological treatment is the St George's Respiratory Questionnaire (SGRQ)[28] which is completed by the patient and has 50 questions covering three areas: symptoms, activity (i.e. limitations) and impacts (of disease), which are summed to provide a total score of between 0 (best) and 100 (worst). This was used in the indacaterol clinical trials.

The threshold for an MCID is a 4-unit decrease in total SGRQ score.[29] For example, a change of this size would occur in a patient who reports that he or she no longer takes so long to wash or dress, can walk up stairs without stopping, and is able to leave the house for shopping or entertainment.[30,31]

Statistical methods

In each of the studies, the primary variable was analysed using a mixed-model analysis of covariance with treatment as a fixed effect and baseline FEV_1 and FEV_1 reversibility as covariates. The same model (with appropriate covariates) was used to analyse the other efficacy variables. The results are presented here as adjusted treatment effects, taking the baseline covariates into account, as least squares means estimates. The number of COPD exacerbations over the length of the study was analysed using a Poisson regression model.

Results

Patient characteristics

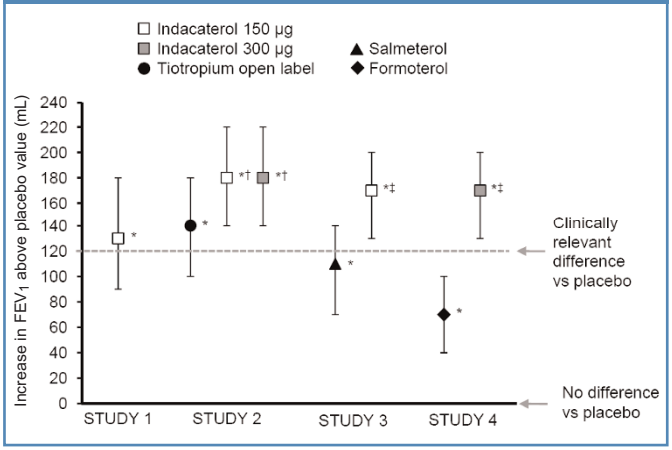
Across the four studies, the population of randomised patients had a mean duration of COPD from diagnosis of seven years and a mean smoking history of 40–57 pack-years. Their mean age was 63–64 years, so approximately half the patients were older than 65. There were more males (52–80%) than females. Between 32% and 53% of patients were also receiving ICS, which they were allowed to continue to use throughout the studies, provided the dose and regimen remained unchanged. Patients on fixed-dose ICS and bronchodilator combinations continued only the ICS component for the duration of the study. Spirometry measurements at baseline showed an FEV_1 of 53–56% predicted and FEV_1/FVC ratio of 0.51–0.53 (both values assessed within 30 min after inhalation of salbutamol 400 µg). Concomitant cardio- or cerebro-vascular conditions were present in 20% of patients, hypertension in 50%, diabetes mellitus in 10%, and hyperlipidaemia in 35%.[32]

Measurements

a) Bronchodilator effect (FEV_1)

Figure 1 shows the 'trough' FEV_1 after 12 weeks of treatment. Only the once-daily bronchodilators (indacaterol and tiotropium) exceeded the 120 mL threshold for clinical relevance pre-specified in these studies. For trough FEV_1 at Week 12, indacaterol 150 and 300 µg were statistically superior to open-label tiotropium, indacaterol 150 µg was

Figure 1. Bronchodilator effect of treatments, shown here as 'trough' forced expiratory volume in 1 s (FEV_1) (measured after 12 weeks of treatment, at 24 h following indacaterol or tiotropium and 12 h following salmeterol or formoterol). Data are least squares mean differences (±95% CI) between active treatments and placebo. Statistically significant differences (p<0.05) are shown compared with *placebo, †tiotropium and ‡salmeterol or formoterol. Study treatments were indacaterol 150 µg or 300 µg once daily, salmeterol 50 µg or formoterol 12 µg twice daily, open-label tiotropium 18 µg once daily, or placebo



statistically superior to salmeterol, and indacaterol 300 µg was statistically superior to formoterol. The efficacy of indacaterol was maintained over the study durations (i.e. six months [Studies 2 and 3[12,13]] and one year [Study 4[14]]).

Indacaterol has a fast onset of bronchodilator effect following the first dose. In the four studies, mean FEV_1 measured at 5 min after the first dose with indacaterol was 110–130 mL greater than after placebo (p<0.001), approximately double the corresponding values with tiotropium (70 mL; p<0.001 vs tiotropium) and salmeterol (60 mL; p<0.001 vs salmeterol), and similar to formoterol (140 mL; not significantly different).

b) Breathlessness

Indacaterol improved breathlessness assessed using the TDI (Figure 2), with an effect close to or greater than the threshold for clinical relevance. Indacaterol had a similar (150 µg dose) or greater (300 µg dose) effect than open-label tiotropium, and a greater effect than the twice-daily bronchodilators formoterol and salmeterol. These differences are evident both in terms of the effect on mean TDI scores (Figure 2a), and the percentage of patients who achieved at least a clinically relevant improvement in breathlessness (Figure 2b). Indacaterol, along with all the other bronchodilators, showed a statistically significant effect compared with placebo at later time points during the 6-month and 1-year studies (Table 2).

c) Use of as-needed salbutamol

Patients treated with indacaterol used less as-needed salbutamol, with a decrease of approximately 1.5 puffs per day from baseline usage. The decrease was greater than that seen for patients receiving either tiotropium or formoterol (Figure 3a). The patients receiving indacaterol also recorded more days when they took no salbutamol – 55-60% of days without salbutamol – which is more than were recorded with tiotropium (46%) and formoterol (52%) (see Figure 3b).

d) Exacerbations of COPD

Exacerbation rates were numerically reduced compared with placebo with all the bronchodilators, but in most cases the effect was not statistically significant (Figure 4). These studies

Figure 2. Effect of treatment on breathlessness (assessed using transition dyspnoea index [TDI]), measured after 12 weeks of treatment as (a) mean score and (b) % of patients responding with a clinically important improvement. Data in (a) are least squares mean differences (±95% CI) between active treatments and placebo. Statistically significant differences (p<0.05) are shown compared with *placebo, †tiotropium and ‡salmeterol or formoterol. Significant differences in (b) were calculated from odds ratios for the likelihood of achieving a clinically important improvement. Study treatments were indacaterol 150 µg or 300 µg once daily, salmeterol 50 µg or formoterol 12 µg twice daily, open-label tiotropium 18 µg once daily, or placebo

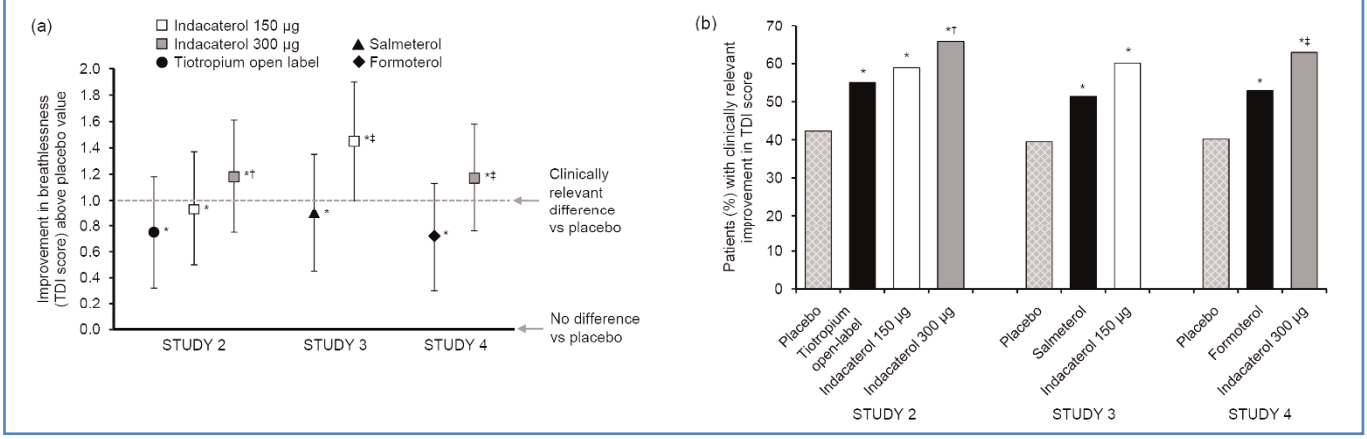


Table 2. Summary of results for breathlessness and health status at each time point in the 6-month (Studies 2 and 3)[12,13] and 1-year studies (Study 4).[14] See Key for explanation of symbols

	Study 2[12]			Study 3[13]		Study 4[14]	
Week	Tio	Ind 150	Ind 300	Salm	Ind 150	Form	Ind 300
Breathlessness (TDI total score)							
4	✓	✓✓	✓✓†	✓	✓‡	✓	✓✓
8	✗	✓	✓✓†	✓	✓	✓	✓✓‡
12	✓	✓	✓✓†	✓	✓✓‡	✓	✓✓‡
24/26	✓	✓✓	✓✓	✓	✓	✓	✓✓‡
44	–	–	–	–	–	✓	✓✓
52	–	–	–	–	–	✓	✓✓
Health-related quality of life (SGRQ score)							
4	✗	✓†	✓†	✓	✓	✓	✓
8	✗	✓†	✓†	✓	✓✓	✓	✓✓‡
12	✗	✓†	✓	✓✓	✓✓‡	✓	✓
24/26	✗	✓†	✓	✓✓	✓✓	✓	✓✓
44	–	–	–	–	–	✓	✓✓
52	–	–	–	–	–	✓✓	✓✓

Key:

✗ = no statistically significant difference versus placebo

✓ = statistically significant improvement versus placebo

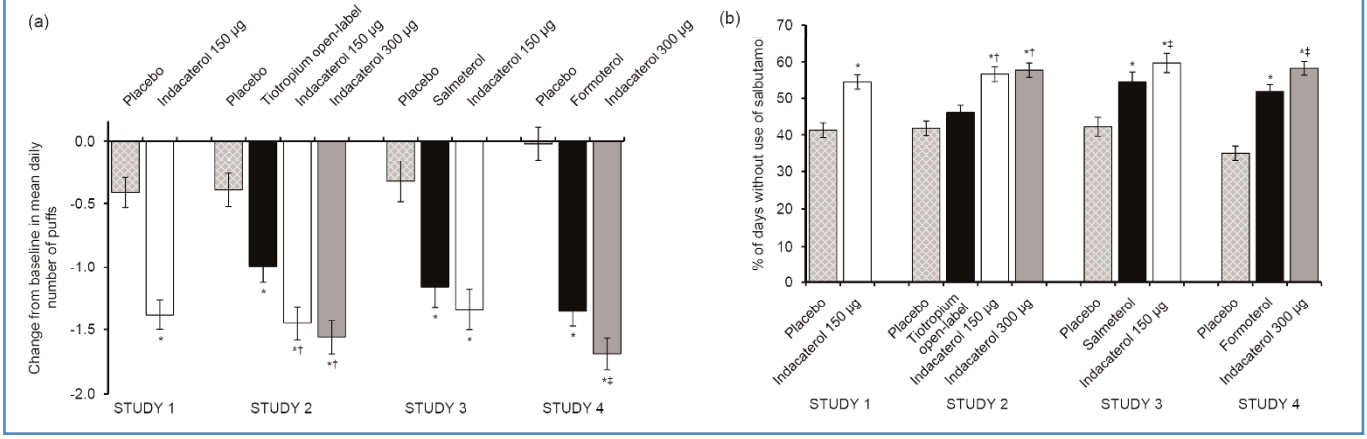
✓✓= statistically significant and clinically relevant improvement versus placebo (clinically relevant difference only applies to TDI and SGRQ scores)

†, ‡ = statistically significant improvement versus †tiotropium and ‡salmeterol or formoterol.

Tio = open-label tiotropium; ind 150 and ind 300 = indacaterol 150 and 300 µg; salm = salmeterol; form = formoterol; TDI = transition dyspnoea index; SGRQ = St George's Respiratory Questionnaire.

Clinically relevant improvement = ≥1 point in TDI total score; ≥4 units in SGRQ total score.

Figure 3. Effect of treatment on use of as-needed salbutamol, averaged over the period of the studies, as (a) change from baseline and (b) days without use of salbutamol. Data are least squares means ±SE. Statistically significant differences (p<0.05) are shown compared with *placebo, †tiotropium and ‡salmeterol or formoterol. Study treatments were indacaterol 150 µg or 300 µg once daily, salmeterol 50 µg or formoterol 12 µg twice daily, open-label tiotropium 18 µg once daily, or placebo

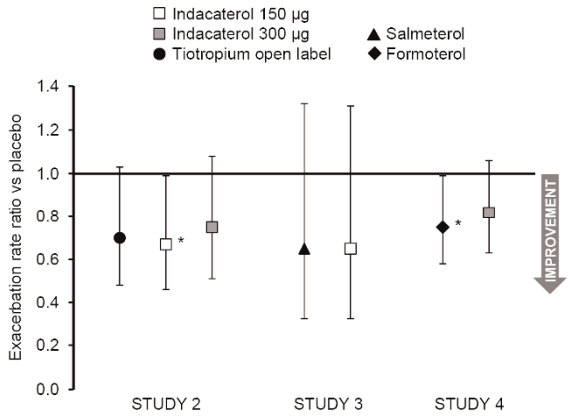


were not designed to measure exacerbations as a primary outcome, so only stable patients were recruited (the annual exacerbation rates with placebo treatment were in the range 0.7–1.0 in the three studies).

e) Health status

Health status, assessed using the SGRQ, was improved relative to placebo with indacaterol and with the two twice-daily bronchodilators, but not with tiotropium (Figure 5), although it must be recalled that tiotropium was given 'open label'. As seen in previous studies with bronchodilators, most treatments did not produce a change that exceeded the MCID when compared with placebo, but this was achieved with indacaterol 150 µg in Studies 1 and 3, and with salmeterol in Study 3 (Figure 5a). A similar pattern of results was seen for the

Figure 4. COPD exacerbation rates in the 6-month and 1-year studies (Studies 2, 3 and 4), plotted as the ratio of exacerbation rate (±95% CI) between active and placebo treatments over the study duration. For example, a rate ratio of 0.5 demonstrates a halving of the exacerbation rate compared with placebo. Statistically significant differences (p<0.05) are shown compared with *placebo. Study treatments were indacaterol 150 µg or 300 µg once daily, salmeterol 50 µg or formoterol 12 µg twice daily, open-label tiotropium 18 µg once daily, or placebo



percentage of patients with a clinically relevant improvement in health status (Figure 5b). Indacaterol 150 µg produced more patients with a clinically significant improvement than did salmeterol. Results for health status at all the time points in the studies are summarised in Table 2.

Efficacy in patients with GOLD II stage COPD

The studies reviewed here included a substantial proportion of patients with severe COPD (GOLD stage III). This is appropriate to primary care, since a recent large European study in primary care found that nearly 40% of patients had GOLD stage III or IV disease.[33] Data from GOLD II patients are rarely presented, so in order to provide information on the effect of treatment on outcomes in such patients, data for the subgroup of patients with GOLD II or less from the studies reviewed (approximately 60% of the total population) were pooled and then analysed. As shown in Figure 6, indacaterol provided statistically and clinically relevant improvements in scores for breathlessness and health status compared with placebo.

Safety

More than 4,000 patients have completed treatment with indacaterol so far in controlled clinical studies of at least 12 weeks' duration, and no significant safety concerns have arisen. Safety has been evaluated during up to one year's treatment with the approved daily doses of 150 and 300 µg, and with a higher (unlicensed) dose of 600 µg once daily. Adverse events generally occurred at a similar incidence in the indacaterol and placebo treatment groups. The most common adverse events reflected the symptoms and manifestations of COPD, such as worsening of COPD and respiratory tract infections. As with the other long-acting bronchodilators[9,34–37] indacaterol has a good profile of cardiovascular safety in patients with COPD, and has little or no effect on vital signs and QTc interval, the derived ECG measurement used to indicate risk of arrhythmias.[32] Approximately 20% of patients experience a mild transient cough in the first few minutes after inhalation of indacaterol. This typically lasts for several seconds and is not associated with loss of efficacy, increased dropout rates or with any safety concerns.[11–14]

Figure 5. Effect of treatment on health status (assessed using St George's Respiratory Questionnaire [SGRQ]), measured after 12 weeks of treatment as (a) mean score and (b) % of patients responding with a clinically important improvement. Data in (a) are least squares mean differences (±95% CI) between active treatments and placebo. Statistically significant differences (p<0.05) are shown compared with *placebo, †tiotropium and ‡salmeterol or formoterol. Significant differences in (b) were calculated from odds ratios for the likelihood of achieving a clinically important improvement. Study treatments were indacaterol 150 µg or 300 µg once daily, salmeterol 50 µg or formoterol 12 µg twice daily, open-label tiotropium 18 µg once daily, or placebo

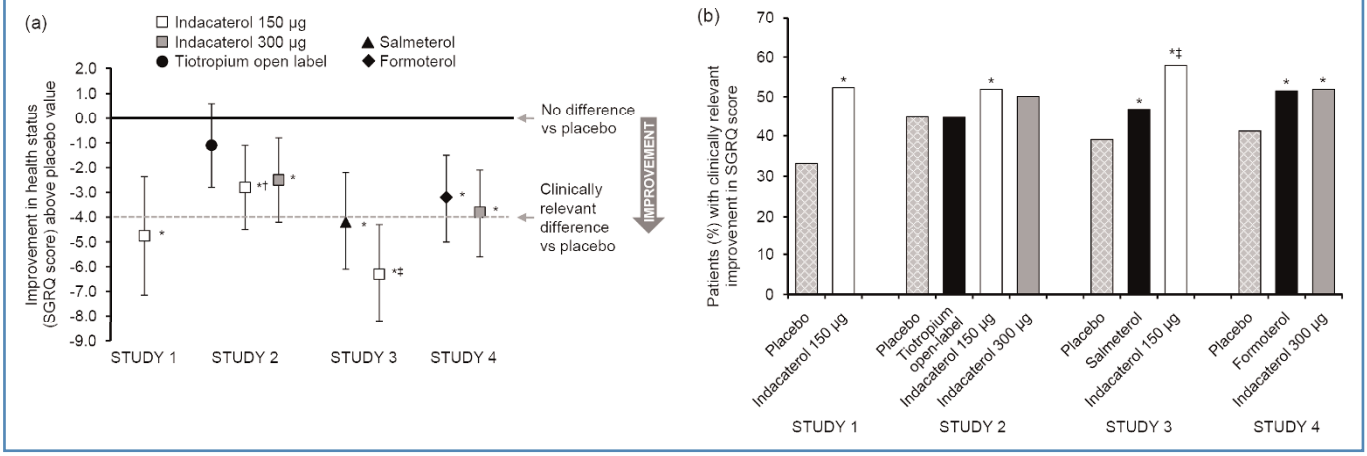
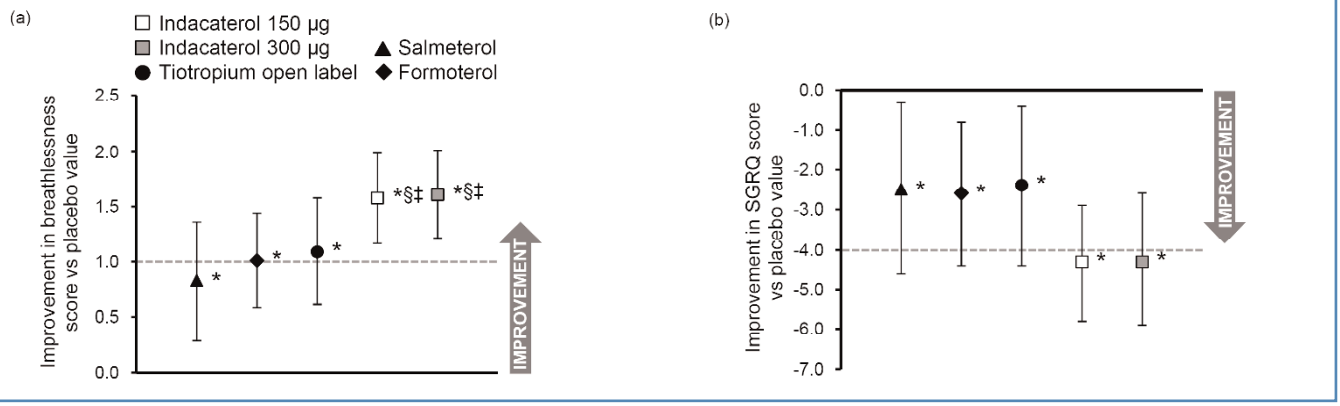


Figure 6. Effect of treatment on (a) breathlessness (assessed using transition dyspnoea index, TDI) and (b) health status (St George's Respiratory Questionnaire, SGRQ) in patients with moderate or less (GOLD I or II) COPD after 12 weeks, using pooled data from studies 1–4. Data are least squares mean differences (±95% CI) between active treatments and placebo. Statistically significant differences (p<0.05) are shown compared with *placebo, §salmeterol or ‡formoterol. Dotted lines show threshold for clinically relevant improvement compared with placebo. Study treatments were indacaterol 150 µg or 300 µg once daily, salmeterol 50 µg or formoterol 12 µg twice daily, open-label tiotropium 18 µg once daily, or placebo



Summary of risk:benefit ratio

Bronchodilators are recommended as part of COPD management for their effectiveness not only in increasing lung function but also for improvements in symptoms, activities of daily living and exercise capacity.[1,2] Indacaterol provides a level of bronchodilation that is similar to tiotropium and greater than the twice-daily agents, formoterol and salmeterol. The measures of breathlessness and health status used in the indacaterol studies encompass components reflecting symptoms and the ability to undertake activities of daily living. Indacaterol was effective at reducing breathlessness, the most troublesome COPD symptom,[20] and the 300 µg dose was significantly more effective in this regard than tiotropium and the twice-daily agents. Indacaterol also performed most effectively overall in terms of improving health status compared with the other agents. The beneficial effects of indacaterol on breathlessness and health status in GOLD II patients suggest that the overall study results provide a useful guide to the level of efficacy that may be expected in the milder patients who may be seen predominantly in a primary care patient population.

The effect of indacaterol on exacerbations was inconsistent in this relatively stable population of patients with low numbers of exacerbations. It is possible that indacaterol (like tiotropium[38,39]) will prove effective in studies specifically designed to examine its effect on exacerbations. Indacaterol has a good safety profile that compares well with the other bronchodilators. We believe that indacaterol provides worthwhile benefit in terms of symptom improvement with minimal risk.

Some questions are not resolved by the four studies reviewed here. For example, what is the optimum initial dose of indacaterol? What is the drug's effect on hyperinflation? – one of the key factors in causing breathlessness in COPD. While the usual starting dose of indacaterol is 150 µg once daily, the 300 µg dose may provide additional clinical benefit with regard to breathlessness, especially in patients with more severe disease.[12] The effects of indacaterol on hyperinflation were addressed by two recent placebo-controlled studies in which indacaterol 300 µg improved lung hyperinflation at rest and during exercise, increased exercise capacity, and reduced breathlessness on exertion.[40,41]

Place of indacaterol in treatment algorithm

A patient with confirmed COPD who remains troubled by symptoms that limit their daily activities despite using a short-acting bronchodilator is a candidate for long-acting bronchodilator treatment. Factors to consider are the patient's symptomatic response and preference, and the drug's side effects and cost. Indacaterol has attractions as a once-daily bronchodilator as it has slightly greater efficacy than twice-daily bronchodilators. It has been suggested that a once-daily regimen may improve adherence,[18] although this remains to be proven in well-conducted studies.

Comparing indacaterol with tiotropium is complicated by the fact that tiotropium treatment was not blinded in Study 2. Whilst this raises the possibility of bias in the measured effects with tiotropium (in either a positive or negative direction), the authors of the study concluded that indacaterol was at least as effective as tiotropium.[12] A blinded 12-week study in 1,598 patients comparing indacaterol 150 µg with tiotropium, in which treatment assignment was blinded, found that although the two treatments had closely similar bronchodilator effects (on trough FEV_1), indacaterol had a statistically significantly better effect on breathlessness (TDI scores), use of as-needed

salbutamol, and health status (SGRQ scores).[42] On the other hand, tiotropium has established efficacy in reducing COPD exacerbations,[38,39] while the efficacy of indacaterol in this respect has not yet been fully investigated.

On balance, indacaterol would be a reasonable first choice for maintenance bronchodilator therapy and the option to increase the dose may be useful if the patient continues to experience breathlessness. Tiotropium has one approved daily dose and is a good alternative. As a further option for stepping up treatment, the two agents could be administered concomitantly and would be expected to provide greater efficacy than either alone.[2] Future treatment algorithms may expand to include combinations of once-daily anticholinergic and β_2-agonist bronchodilators, as recently reported.[43]

Whilst long-acting bronchodilators, alone or in combination, are the initial maintenance treatment of choice in COPD,[2] patients presenting with a history of frequent exacerbations and severely impaired lung function, or who exacerbate frequently while on bronchodilator therapy, may benefit from ICS treatment, which has been shown to be effective in reducing exacerbations.[5,44–47] Roflumilast (an oral phosphodiesterase-4 inhibitor) is also approved for use in this situation in selected patients,[48] but there are several precautions that need to be taken for its safe use[49] and patients therefore need to be carefully evaluated to ensure they meet the necessary criteria.[49,50]

Summary

Effective bronchodilation is likely to help patients with COPD to stay active and productive, and is an important element of treatment. Indacaterol has been shown to provide sustained bronchodilation with a fast onset on the first dose, together with reduced breathlessness and improved health status compared with placebo over a period of up to one year. Indacaterol was also shown to provide symptomatic improvements similar to those of tiotropium. On the basis of the evidence reviewed, we conclude that once-daily indacaterol is an effective and beneficial maintenance bronchodilator treatment for patients with moderate-to-severe COPD, including patients with GOLD stage II.

Handling editor

David Bellamy

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Conflicts of interest

PWJ has received consultancy fees from Novartis and GlaxoSmithKline (GSK) and has sat on advisory boards for GSK, AstraZeneca (AZ), Roche, Boehringer-Ingelheim (BI), Forest, Almirall, and Spiration. He has received grants from GSK.

NCB has provided ad hoc consultancy advice to the following companies with an interest in asthma: AZ, Chiesi, GSK, Novartis, Teva, Shire Pharmaceuticals, Merck Sharp & Dohme (MSD). He has given lectures for AZ, Chiesi, GSK, MSD, Novartis, and has received research funding which has gone into departmental funds from AZ, GSK, MSD and Novartis. Neither he nor any relative hold shares in the pharmaceutical industry.

CV has received fees for presentations at symposia sponsored by (in alphabetical order) AZ, BI, Chiesi, GSK, Janssen-Cilag, Novartis, Nycomed, Pfizer, Talecris, and for consulting from (in alphabetical order) AZ, BI, GSK, Janssen-Cilag, Novartis, Nycomed, and Talecris.

DL and BK are employees of Novartis.

Contributorship

DL and BK made substantial contributions to the conception and design of the four studies described in this manuscript. NCB and CV were involved in the acquisition of data and PWJ in the interpretation of data in the original studies. DL was responsible for analysis of data. All authors were involved in the concept and design of this article and the interpretation of the data, and had full access to the primary study data. All authors revised the article critically for important intellectual content, and gave their final approval of the version to be published.

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