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Effects of long-acting bronchodilators in COPD patients according to COPD severity and ICS use

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Summary
Background: Indacaterol is a once-daily, long-acting β_2-agonist bronchodilator that improves dyspnoea and health status in patients with moderate-to-severe COPD. While its bronchodilator effects have been shown to be maintained in different patient subgroups, effects on clinical outcomes in certain subgroups are not yet defined.
Methods: Post-hoc analysis of pooled clinical study data to investigate efficacy and safety of indacaterol compared with placebo and other long-acting bronchodilators (formoterol, salmeterol, open-label tiotropium) in patient subgroups defined by COPD severity (GOLD stage II or III; $n = 4082$) and ICS use at baseline (no/yes; $n = 4088$). Efficacy outcomes were trough (24-h post-dose) FEV_1, dyspnoea (transition dyspnoea index; TDI) and health status (St George's Respiratory Questionnaire; SGRQ) after 26 weeks.
Results: All active treatments significantly improved trough FEV_1 and dyspnoea compared with placebo, and all apart from open-label tiotropium improved health status compared with placebo. Among active treatments, indacaterol 150 μg had the best overall efficacy profile in the GOLD II and no-ICS subgroups. In the GOLD III and ICS subgroups, indacaterol 300 μg had the best overall efficacy, including a marked effect on dyspnoea (1.4-point improvement in TDI total score vs. placebo; $p < 0.001$). Within subgroups, the incidence of adverse events was similar between treatments.

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Conclusion: Indacaterol maintained its efficacy regardless of disease severity or use of concurrent ICS. Indacaterol 150 μg had the best overall efficacy profile in the GOLD stage II patients while, in patients with more severe disease, indacaterol 300 μg provided useful improvements in dyspnoea.

Introduction

Inhaled long-acting bronchodilators feature prominently among the recommended pharmacological treatments for the management of patients with chronic obstructive pulmonary disease (COPD).[1] Available long-acting bronchodilators include the twice-daily long-acting β_2-agonists (LABAs) formoterol and salmeterol, the once-daily long-acting antimuscarinic (LAMA) tiotropium and, more recently, the once-daily LABA indacaterol.

In placebo-controlled clinical studies, indacaterol has demonstrated beneficial effects on lung function, symptoms and health status in patients with moderate-to-severe COPD.[2–5] Most of the clinical trials with indacaterol have included broadly similar proportions of patients with moderate and severe COPD and similar proportions of patients receiving concomitant inhaled corticosteroids (ICS) or not at baseline. Many of the pivotal placebo-controlled studies with indacaterol included pre-specified analyses of the primary efficacy outcome (trough FEV_1 after 12 weeks of treatment) in patient subgroups defined according to factors such as COPD severity, use of ICS, age and smoking status. Adverse event data were also summarised for the subgroups. The results showed that indacaterol maintained a significant bronchodilator effect[3,4] and a similar level of adverse events in these subgroups. We report here on the results of a post-hoc analysis conducted with the aim of exploring further the effects of indacaterol in patient subgroups defined according to COPD severity and ICS use at baseline, evaluating both bronchodilator effects and clinical outcomes (dyspnoea and health status) over a treatment period of 6 months. The analysis was performed using data from more than 4000 patients pooled from three pivotal clinical studies that included comparisons with the other available long-acting inhaled bronchodilators: tiotropium, salmeterol and formoterol, all of which have been published individually.[3–5]

Methods

Patients

The studies enrolled men and women aged ≥40 years with a diagnosis of moderate-to-severe COPD (post-bronchodilator FEV_1 <80% and ≥30% predicted and FEV_1/FVC <70%; GOLD 2005 criteria), with a smoking history of ≥20 pack-years. Patients with a recent respiratory tract infection or COPD exacerbation were not included. Concomitant ICS use was allowed but the dose and regimen had to remain stable for the duration of each study. Patients who were receiving LABA/ICS fixed-dose combinations prior to the study were switched to equivalent ICS monotherapy. Patients were allowed to use short-acting β_2-agonists for symptom relief as needed during the studies.

Study design

Data were pooled from three randomised, double-blind, placebo-controlled studies. Full details of the individual studies have been published previously.[3–5] The first was a 6 month study (NCT00567996) comparing indacaterol 150 μg once daily with placebo and salmeterol 50 μg twice daily, all given double-blind.[5] The second was a 1 year study (NCT00393458) comparing indacaterol 300 μg once daily with placebo and formoterol 12 μg twice daily, all given double-blind (6 month data were included in the present analysis).[3] The third was a 6 month study (NCT00463567) comparing indacaterol 150 μg and 300 μg with placebo (double-blind) and open-label tiotropium 18 μg, once daily.[4] The primary efficacy variable in each of those studies was forced expiratory volume in 1 s (FEV_1) at 'trough' (24 h following the previous morning dose of indacaterol or tiotropium and 12 h following the previous evening dose of formoterol or salmeterol) after 12 weeks' treatment.

Assessments and variables

In the present analysis, efficacy was assessed after 26 weeks' treatment. Using standardised spirometry,[6] the bronchodilator effect was measured as trough FEV_1. Dyspnoea was measured as transition dyspnoea index (TDI) total score and the percentage of patients responding with a minimum clinically important difference (MCID; improvement of ≥1 point) in TDI total score, with associated odds ratios.[7–9] Health status was measured using St George's Respiratory Questionnaire (SGRQ) total score and the percentage of patients responding with the MCID of ≥4 units in SGRQ total score, with associated odds ratios.[10,11] Adverse events were recorded and summarised.

Statistical analysis

Patients were divided into subgroups of GOLD stages II and III, irrespective of ICS use, and into subgroups according to ICS use, irrespective of GOLD stages. In each subgroup (GOLD stages and ICS use) we performed separate statistical analyses.

Trough FEV_1 after 26 weeks of treatment was analysed using a mixed-model analysis of covariance with treatment as a fixed effect and baseline FEV_1 and baseline FEV_1 reversibility (to salbutamol and to ipratropium) as covariates. The same model (with appropriate covariates) was used to analyse the TDI and SGRQ efficacy variables. Missing TDI and SGRQ data were imputed with the last observation (provided this was within the last 11 weeks) carried forward. No powering or sample size calculations were performed for this post-hoc analysis, although all