



HAL
open science

Immediate salbutamol responsiveness does not predict long-term benefits of indacaterol in patients with chronic obstructive pulmonary disease

Pierre-Régis Burgel, Vincent Le Gros, Laurent Decuyper, Isabelle Bourdeix, Thierry Perez, Gaetan Deslée

► To cite this version:

Pierre-Régis Burgel, Vincent Le Gros, Laurent Decuyper, Isabelle Bourdeix, Thierry Perez, et al.. Immediate salbutamol responsiveness does not predict long-term benefits of indacaterol in patients with chronic obstructive pulmonary disease. *BMC Pulmonary Medicine*, 2017, 17, pp.25. 10.1186/s12890-017-0372-z . hal-02451056

HAL Id: hal-02451056

<https://hal.univ-reims.fr/hal-02451056>

Submitted on 3 Jun 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.


L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

RESEARCH ARTICLE

Open Access



Immediate salbutamol responsiveness does not predict long-term benefits of indacaterol in patients with chronic obstructive pulmonary disease

Pierre-Régis Burgel^{1*} , Vincent Le Gros², Laurent Decuyper², Isabelle Bourdeix², Thierry Perez³ and Gaëtan Deslée⁴

Abstract

Background: The purpose of this study was to evaluate the correlation between immediate responsiveness with the short-acting β_2 -agonist salbutamol and effects of treatment with the ultra-long-acting β_2 -agonist indacaterol in patients with chronic obstructive pulmonary disease (COPD).

Methods: The REVERBRESZ study was a phase IV, multicentre, open-label study in which patients with moderate-to-severe COPD received indacaterol 150 μ g once-daily for 5 months. The primary endpoint was the correlation between immediate response of forced expiratory volume in 1 s (FEV₁) post-inhalation of salbutamol (400 μ g) at study entry and the change from baseline in trough FEV₁ after 1 month of indacaterol. Secondary endpoints included dyspnoea measured by the modified Medical Research Council (mMRC) grade and health-related quality of life measured by the clinical COPD questionnaire (CCQ).

Results: Of the 602 patients enrolled from 177 centres in France, 543 patients received at least one indacaterol dose, 512 patients completed 1 month of indacaterol treatment (primary endpoint), and 400 patients completed 5 months of treatment. At study entry, mean FEV₁ values before and after salbutamol inhalation were 1.54 ± 0.50 L and 1.65 ± 0.53 L, respectively. Based on the magnitude of an immediate response of FEV₁ after salbutamol inhalation at study entry, patients were classified into reversible (Rv, $\geq 12\%$ and ≥ 200 mL from pre-salbutamol value; $n = 106$) and non-reversible (NRv, $< 12\%$ or < 200 mL from pre-salbutamol value; $n = 431$) groups. After 1 month of indacaterol treatment, mean absolute and relative difference in trough FEV₁ were 100 mL and 9%, respectively. No significant correlation was found between the immediate FEV₁ response to salbutamol at study entry and change from baseline in trough FEV₁ after 1 month of indacaterol treatment (correlation coefficient = 0.056 [95% CI; -0.032, 0.144] for absolute response and 0.028 [95% CI; -0.06, 0.116] for relative response). At all subsequent visits, mMRC and CCQ scores, and FEV₁ improved from baseline with no significant difference between the Rv and NRv groups.

Conclusions: Immediate FEV₁ response to salbutamol did not predict the long-term benefits observed with indacaterol treatment in patients with COPD. Patients considered reversible or non-reversible to salbutamol showed comparable improvements in lung function, dyspnoea and health-related quality of life.

Trial registration: ClinicalTrials.gov: NCT01272362. Date: January 5, 2011

Keywords: COPD, Indacaterol, Reversibility, Salbutamol

* Correspondence: pierre-regis.burgel@aphp.fr

¹Respiratory Medicine, APHP-Hôpital Cochin-Université Paris Descartes, 27 rue du Faubourg St Jacques, Sorbonne Paris Cité, Paris 75014, France
Full list of author information is available at the end of the article

Background

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is usually progressive and can lead to dyspnoea and impaired quality of life [1, 2]. The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) strategy recommends long-acting bronchodilators for maintenance treatment in patients with moderate-to-severe COPD, as they have been shown to improve lung function, dyspnoea, quality of life and exacerbation rate [2]. Among inhaled long-acting β_2 -agonists (LABAs), salmeterol and formoterol are administered twice-daily and provide bronchodilation for approximately 12 h [3–6], while indacaterol (Onbrez[®] Breezhaler[®]), an ultra-LABA, is administered once daily and provides 24 h of sustained bronchodilation [1].

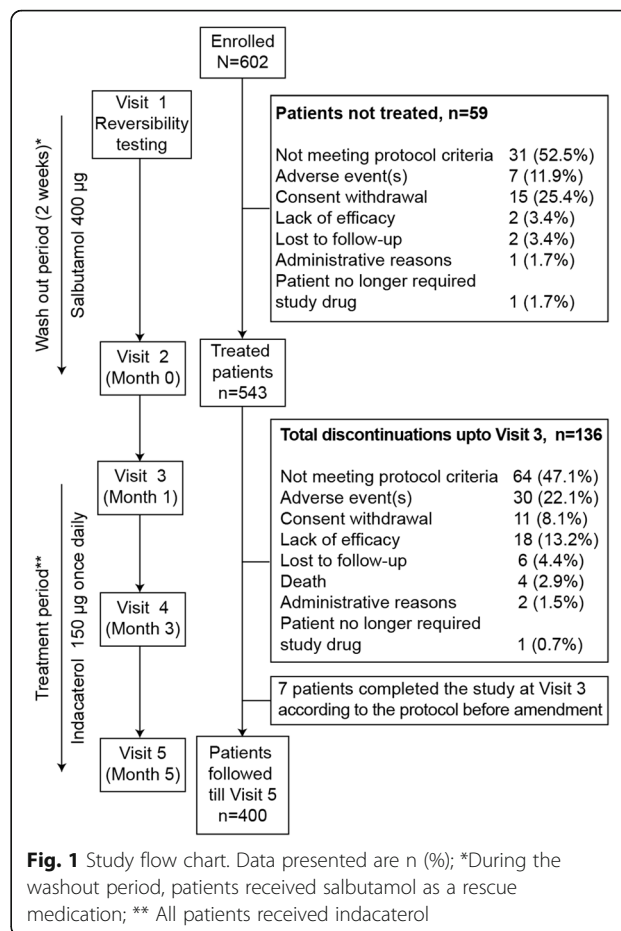
Bronchodilator reversibility testing, despite not being mentioned in the current treatment recommendations [2], is commonly used in daily clinical practice to predict the usefulness of a bronchodilator treatment [2]. Although the test is simple, it is difficult to interpret or rely on because the response may vary depending on the day and time of testing, severity of baseline lung-function impairment, and the number of drugs given to perform the test [2]. Published data further suggests that acute reversibility in response to bronchodilators in patients with COPD does not predict clinical outcomes [7, 8].

The present study evaluated the correlation between the immediate forced expiratory volume in 1 s (FEV₁) response with a short-acting β_2 -agonist, salbutamol 400 μ g (via a metered-dose inhaler), and the clinical and lung function responses to treatment with indacaterol 150 μ g once daily (via the Breezhaler[®] device) after 1–5 months in patients with moderate-to-severe COPD.

Methods

Study design and patients

This was a phase IV, multicentre, open-label study conducted at 177 centres in France between December 2010 and May 2012. Men and women aged ≥ 40 years, with a smoking history of ≥ 10 pack-years and with moderate to severe COPD [9] as defined by a post-bronchodilator FEV₁ $\geq 30\%$ and $< 80\%$ of the predicted value and a post-bronchodilator FEV₁ to forced vital capacity (FVC) ratio < 0.70 , were recruited in the study. Patients were excluded if they had a COPD exacerbation within 6 weeks before entering the study, long-term oxygen therapy, asthma, or any concomitant pulmonary disease. Enrolled patients were evaluated at five study visits (Fig. 1). At Visit 1 (study entry), any long-acting bronchodilator treatments were discontinued. Patients who were using inhaled corticosteroids at study entry were allowed to continue using it throughout the study without modifying the drug dose or regimen. The salbutamol reversibility test was performed during which FEV₁ was measured



30 min after inhalation of four puffs of salbutamol (100 μ g each). Patients were then classified into the reversible (Rv) group, defined by a post-bronchodilator increase in FEV₁ $\geq 12\%$ and ≥ 200 mL from pre-salbutamol value, or non-reversible (NRv) group, as defined by a post-bronchodilator change in FEV₁ $< 12\%$ or < 200 mL from pre-salbutamol value [9–11]. Salbutamol was the only bronchodilator allowed for use during the 2-week washout period. From Visit 2 (baseline) to Visit 5 (at 5 months), indacaterol 150 μ g was administered once daily, preferably in the morning and spirometry was performed before inhalation of indacaterol (for measuring trough FEV₁) at each visit. There was one protocol amendment. During the trial, the committee recommended that 1 month of treatment (till Visit 3) was too short for optimum evaluation of health-related quality of life. The protocol was therefore amended to extend the study duration by 4 months consisting of Visit 4 and Visit 5 (Fig. 1).

Outcomes

Variables were evaluated at each treatment visit (Visit 2 to Visit 5) and the difference from baseline (Visit 2) was

calculated in both the Rv and NRv groups. The primary endpoint of the study was the correlation between the immediate reversibility of FEV₁ 30 min post-inhalation of salbutamol 400 µg at Visit 1 and the change in trough FEV₁ after 1 month of indacaterol treatment (between Visit 3 and Visit 2). Absolute FEV₁ reversibility (expressed in litres) was defined as the difference between FEV₁ before and after salbutamol administration. Relative FEV₁ reversibility (expressed as a percentage value) was calculated as (absolute reversibility/FEV₁ before salbutamol administration) × 100. Secondary endpoints included FEV₁ change across the study (minimal clinically important difference [MCID] ≥ 100 mL improvement), dyspnoea measured by the modified Medical Research Council (mMRC) grade (MCID decrease of ≥ 1 point) [12], and health-related quality of life (HRQoL) measured by the clinical COPD questionnaire (CCQ; MCID decrease of ≥ 0.4 point) [13]. Safety assessments included recording and monitoring of all adverse events (AEs) and serious adverse events (SAEs).

Statistical analysis

A total of 540 patients were necessary to provide at least 80% power to detect a coefficient of correlation between the immediate reversibility at 30 min post-inhalation in FEV₁ with salbutamol 400 µg at Visit 1 and the variation in trough FEV₁ between Visit 3 and Visit 2 of 0.12. Estimating that about 10% of the data would be incomplete, 600 patients were to be included in the study. The intent-to-treat (ITT) population used for evaluation of primary and secondary endpoints included all enrolled patients in the study who received at least one dose of indacaterol 150 µg and for whom at least one endpoint assessment was available after treatment administration. The safety population included all enrolled patients, who received at least one dose of indacaterol 150 µg and for whom at least one tolerability assessment was available after treatment administration. Descriptive statistics were used for all analyses. The 95% confidence intervals (CI) were provided for main assessment criteria. Statistical tests between the Rv and NRv groups (Chi-square or Wilcoxon rank sum test, according to the variables) were bilateral with a significant threshold of 0.05. However, as there was no comparison group in this study, analyses were exploratory and descriptive and *p*-values were provided only as an indication. All analyses were carried out using SAS v8.2.

Results

Of the 602 patients enrolled, 543 patients received at least one dose of indacaterol, 512 patients completed the study for the primary efficacy endpoint (Visit 3) and 400 patients were followed-up for 5 months (Fig. 1). Of the 195 (32.4%) patients who discontinued the study, 59

patients discontinued between Visit 1 and Visit 2 and did not receive indacaterol; and 136 patients discontinued between Visit 2 and Visit 3. Additionally, 7 patients completed the study at Visit 3 according to the protocol before amendment. Reasons for study discontinuation are listed in Fig. 1.

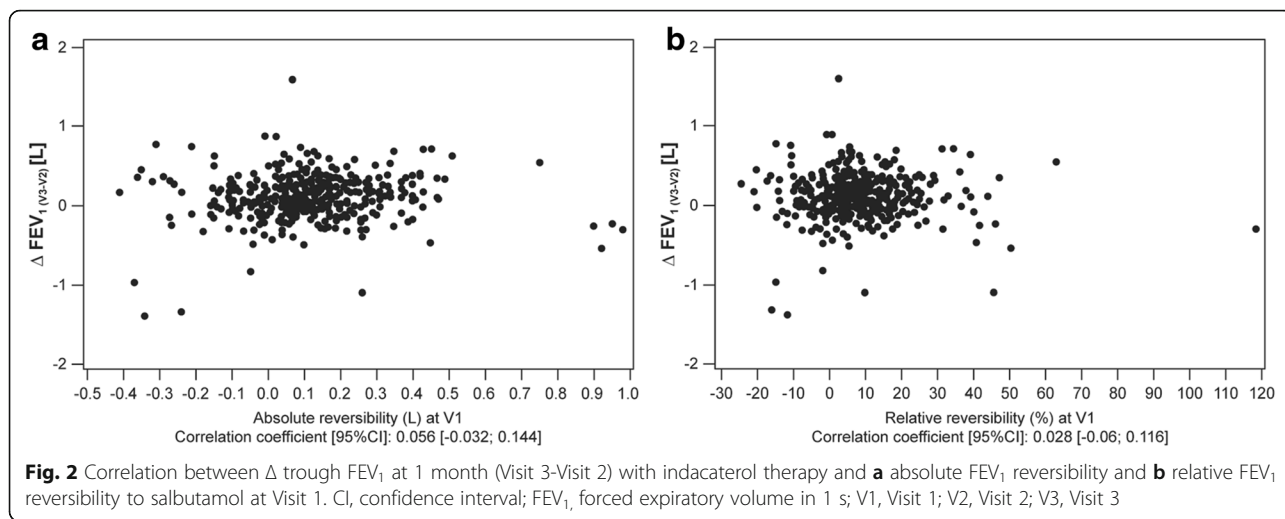
Clinical characteristics of the treated patients (*n* = 543) are presented in Table 1. The mean age was 63 years, and most patients were men (74%) and ex-smokers (64%). The mean ± SD FEV₁ values before and after salbutamol inhalation were 1.54 ± 0.50 L and 1.65 ± 0.53 L, respectively. Of the 543 treated patients, 6 patients had non-interpretable reversibility results. In patients with interpretable reversibility results, 106 patients (20%, Rv group) showed significant FEV₁ reversibility with salbutamol, and 431 patients (80%, NRv group) showed non-significant reversibility. Baseline demographics and patient characteristics were comparable between the Rv and NRv groups (Table 1) and there was no difference in the use of inhaled corticosteroids between these groups.

In patients who received indacaterol, mean absolute and relative improvements in FEV₁ after 1 month of indacaterol treatment (Visit 3-Visit 2) were 100 (±260) mL and 9 (±19) %, respectively. No statistically significant correlation was observed between the change in trough FEV₁ at 1 month and absolute or relative reversibility with salbutamol at study entry (Fig. 2a and b). Improvements in trough FEV₁ from baseline was observed in both the Rv and NRv groups at all visits (Fig. 3a) with no statistically significant difference between the groups

Table 1 Demographics and baseline characteristics of patients who received at least one dose of indacaterol

Variables	Total population (<i>N</i> = 543) ^a	Rv group (<i>n</i> = 106)	NRv group (<i>n</i> = 431)
Age, years	62.7 (9.6)	60.8 (9.9)	63.2 (9.5)
Male, <i>n</i> (%)	404 (74.4)	80 (75.5)	319 (74.0)
Current smoker, <i>n</i> (%)	196 (36.1)	43 (40.6)	151 (35.0)
Number of pack years	40.3 (19.3)	42.2 (20.7)	39.8 (19.0)
Years with COPD	9 (7.4)	9.9 (8.2)	8.8 (7.1)
Post-bronchodilator FEV ₁ (L)	1.65 (0.53)	1.88 (0.51)	1.59 (0.52)
Post-bronchodilator FEV ₁ (L), % predicted	57.3 (14.12)	62.8 (12.24)	55.9 (14.23)
Post-bronchodilator FVC (L)	3.01 (0.82)	3.36 (0.84)	2.92 (0.80)
FEV ₁ /FVC (%) (Visit 2)	53.5 (14.15)	53.3 (10.80)	53.4 (14.89)
mMRC score (Visit 2)	1.4 (0.84)	1.3 (0.85)	1.4 (0.84)
CCQ score (Visit 2)	2.0 (0.99)	1.9 (0.93)	2.0 (1.01)

^a 6 patients had non interpretable reversibility data; Data are presented as mean (SD) unless otherwise specified; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, medical Modified Research Council; SD, standard deviation

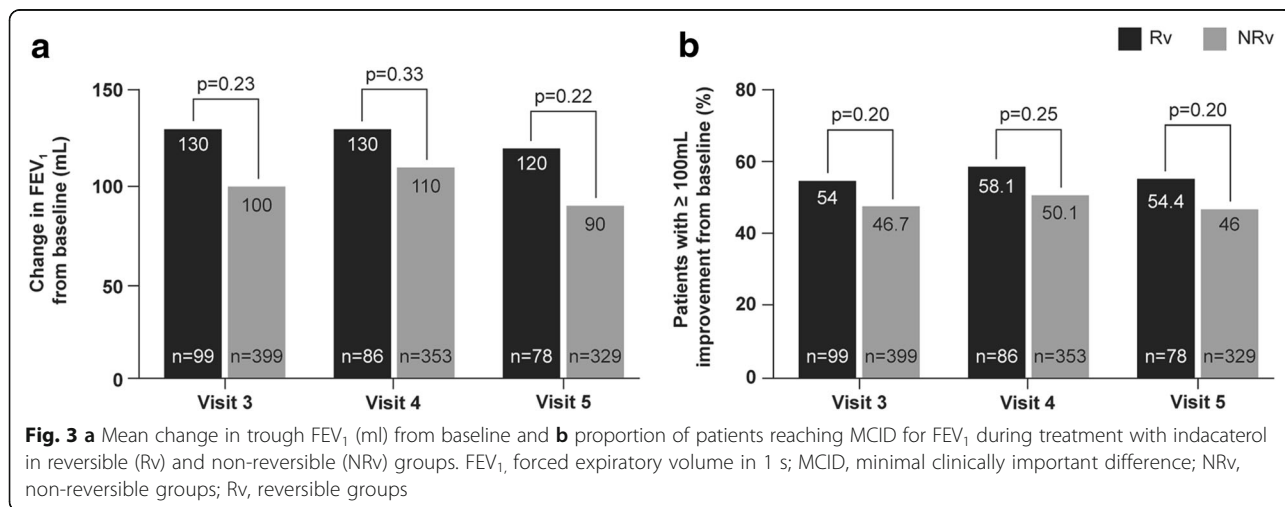


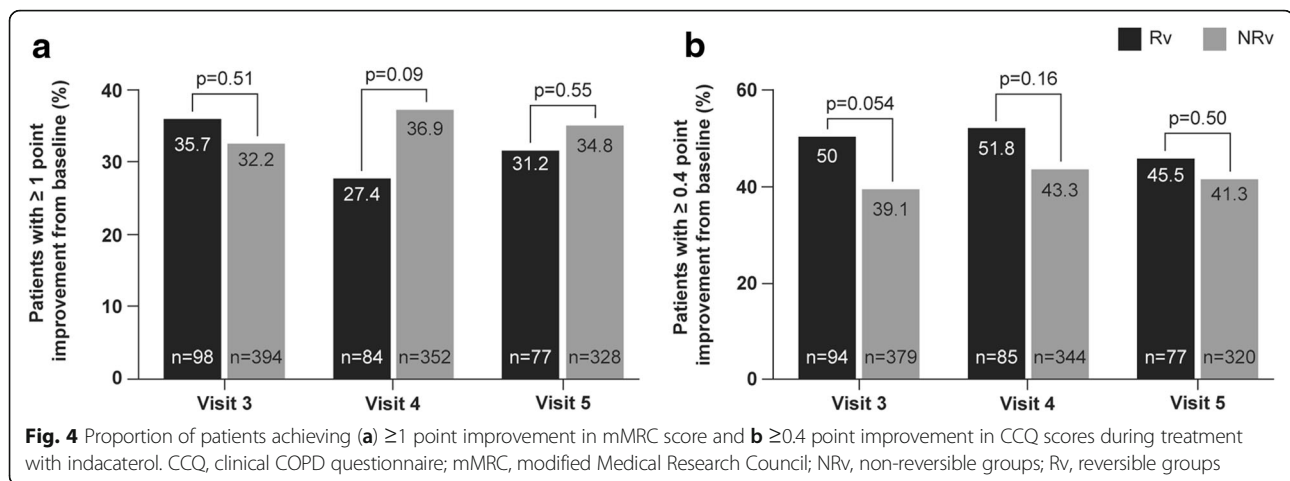
at any visit. The proportion of patients reaching MCID (≥ 100 mL improvement) for FEV₁ at each visit was comparable in both groups (Fig. 3b).

Dyspnoea as measured by mMRC (mean difference in mMRC ranged from -0.3 to -0.2 , *data not shown*) improved in both the Rv and NRv groups at all visits, and there were no statistically significant differences between these groups at any visit. The percentage of patients with a Δ mMRC ≥ 1 from baseline was comparable between the Rv and NRv groups at all visits (Fig. 4a). CCQ scores improved from baseline in both the Rv and NRv groups at all visits with no statistically significant differences between the groups at any visit (*data not shown*). The percentage of patients reaching the MCID in terms of Δ CCQ ≥ 0.4 (Fig. 4b) from baseline was not significantly different between the two groups at any visit.

Of the 543 patients included in the safety analysis, 264 (48.6%) and 33 (6.1%) patients experienced at least one

AE and SAE, respectively. Fifty-two (10%) patients reported at least one AEs that was suspected to be related to the study medication: Rv, $n = 15$ (14.2%) vs. NRv, $n = 37$ (8.6%), $p = 0.10$. Among the AEs (i.e., with a frequency $> 2\%$) COPD exacerbations, bronchitis, and rhinitis were not different between the Rv and NRv subgroups ($p > 0.40$). Compared to the NRv group, patients in the Rv group experienced cough more frequently (9.4% vs 4.6%; $p = 0.02$) and a trend towards more frequent dyspnoea (8.5% vs 4.6%; $p = 0.07$). The incidence of SAEs were low and comparable between the Rv and NRv groups: Rv, $n = 6$ (5.7%) vs NRv, $n = 27$ (6.3%). Overall, four deaths were reported in the study. Two of these deaths (one death after a COPD exacerbation and one sudden death) were assessed by an investigator as suspected to be related to study treatment. The other two deaths (one sudden death because of an unknown cause, and one suicide) were determined as not related to study treatment.





Discussion

The present study showed no correlation between the immediate FEV₁ response with the short-acting β_2 -agonist salbutamol and the change in trough FEV₁ after 1-month of treatment with indacaterol 150 μ g in patients with moderate-to-severe COPD. When patients were subdivided into the Rv and NRv groups (based on response to salbutamol at study entry), there was no significant difference in the improvement in trough FEV₁ after 1 month of treatment with indacaterol. Similarly, no statistically significant difference was observed between the Rv and NRv groups over the 5 months of this study. Although numerical improvements in mMRC and CCQ scores from baseline occurred in both groups, no clinically significant difference was observed between the Rv and NRv groups at any visit. These results suggest that salbutamol responsiveness does not predict the long-term lung function or clinical responses to indacaterol.

These findings are consistent with a previous study with another LABA (formoterol) that also reported no significant correlation between reversibility with salbutamol and clinical efficacy after 1 month of treatment in patients with stable COPD [7]. Similar results were reported after treatment with a long-acting antimuscarinic agent in the Understanding Potential Long-term Improvements in Function with Tiotropium (UPLIFT) trial, which demonstrated that acute bronchodilator responsiveness at baseline did not predict long-term clinical response to tiotropium after 4 years of treatment [14]. Tashkin et al. showed that irrespective of the presence of short term response to tiotropium on day 1, treatment with tiotropium over a 1-year period resulted in significant improvement in FEV₁ compared to baseline in both the responsive and poorly responsive groups, with significant but low correlation ($r = 0.43$) at the end of the study [15]. Our data corroborates the previous findings by showing the absence of a relationship

between acute effects of salbutamol and long term effects of indacaterol, confirming that acute bronchodilator responsiveness should not be used to predict the effects of long-acting bronchodilators.

Results from the present study concur with the GOLD strategy and the other discussed studies [7, 14, 15], acknowledging that the magnitude of reversibility of airflow limitation following inhaled short-acting bronchodilators does not predict the response to long-term treatment with bronchodilators [9]. Non-reversibility of airflow limitation has been used as an inclusion criterion in many COPD studies until recently, however analyses of results from several large studies have concluded that reversibility in COPD patients is a continuous variable. Further, results of reversibility testing vary between tests, time of test, and baseline values and thus should not be used to select patients in a clinical trial or for determining the treatment [16]. It has been also been shown that bronchodilator reversibility is not reproducible over time and does not predict disease progression or mortality [7]. In addition, the current thresholds for spirometric measurements for reversibility are also debatable. Some authors argue that these tests may produce false positive results when the baseline FEV₁ value is low, and that FEV₁ measurements are not always repeatable due to noise effects that can be >100 mL [13, 14, 16–18]. However, others have suggested a lower threshold than the fixed 12% and 200 mL European Respiratory Society (ERS)/American Thoracic Society (ATS) criteria, particularly in patients with low baseline FEV₁ [10]. Pellegrino et al. suggested that any threshold for reversibility testing will have pros and cons, since most proposed thresholds are within the natural variability of FEV₁ and may not be applicable to all disease conditions [19]. Although, the present findings are not in favour of recommending spirometry use for predicting clinical response, there is an ongoing debate around the use of spirometry to assess bronchodilator response [9, 19, 20]. Till date, only

short-acting bronchodilators (e.g. salbutamol) are used for immediate reversibility testing, and we cannot exclude a significant relationship between FEV₁ change at first dose of indacaterol, due to its rapid onset of action, and long term response, as demonstrated with tiotropium [15].

In this study, indacaterol was well tolerated with only 6.1% of patients reporting at least one SAE. The safety profile was consistent with previous indacaterol studies with approximately 5% of patients experiencing cough. Interestingly, cough was more prevalent in patients in the Rv group compared with the non-Rv group. Although these findings require confirmation, they suggest that bronchial responsiveness may favour cough induced by indacaterol. Of the four deaths reported in the study, two (one death of unknown cause and one following COPD exacerbation) were suspected to be related to the study drug. Sudden deaths are not rare in patients with COPD, and severe COPD exacerbations may be fatal [21, 22].

The strengths of the present study are that the response to indacaterol was studied by measuring FEV₁ and validated tools (mMRC scale and CCQ questionnaire) for measuring patient-related outcomes under real-life conditions. We also recognise some limitations to this approach. Although the mMRC scale is easy to use and is widely recommended for evaluating dyspnoea in COPD patients in daily practice [9], it has the major disadvantage of being poorly responsive to therapeutic interventions, including bronchodilators and rehabilitation. This was also the case in the present study, despite a significant proportion of responders, when assessed by using the CCQ and MCID. CCQ appears more responsive than the mMRC scale in this real-life study. A comprehensive symptom assessment is also recommended in addition to measuring breathlessness, using either the COPD assessment test (CAT) or CCQ [9], but the knowledge regarding responsiveness of these short questionnaires to pharmacotherapy remains limited. Interestingly, the percentage of responders for HRQoL in the present real-life study was close to those in the active treatment arms of placebo-controlled studies using the reference St. George Respiratory Questionnaire (SGRQ) [23] [24], confirming the validity of these findings in this non-placebo-controlled trial. The goal of the present study was to evaluate the effects of indacaterol in daily practice in symptomatic patients with post-bronchodilator FEV₁/FVC < 0.70, the diagnostic criteria for COPD according to the GOLD document. Because FEV₁/FVC ratio usually declines with age, some subjects with FEV₁/FVC < 0.7 have a FEV₁/FVC above the lower limit of the age-related predicted value (also called lower limit of normal, LLN) and may not be affected by COPD [25]. Specifically-designed studies with sufficient statistical power will be necessary to examine the effect of bronchodilators on

symptoms in these latter patients. Finally, there were high rates of study discontinuation, mostly due to violation of inclusion criteria and withdrawal of patient consent. Such findings are usual in phase IV studies and are unlikely to affect our conclusions.

Conclusion

In patients with COPD treated with indacaterol for 5 months, immediate FEV₁ reversibility with salbutamol at baseline did not predict the sustained response to indacaterol in terms of lung function, health-related quality of life or dyspnoea.

Abbreviations

AE: Adverse event; CAT: COPD assessment test; CCQ: Clinical COPD questionnaire; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; FEV₁: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GOLD: Global initiative for chronic obstructive lung diseases; HRQoL: Health-related quality of life; ITT: Intent-to-treat; LABAs: Long-acting β_2 -agonists; MCID: Minimal clinically important difference; mMRC: Modified medical research council; NRv: Non-reversible; Rv: Reversible; SAE: Serious adverse event; SGRQ: Saint George respiratory questionnaire; UPLIFT: Understanding potential long-term improvements in function with Tiotropium

Acknowledgements

The authors thank the patients who participated and the staff at the participating clinical centres. Scientific writing support in the preparation of the manuscript was provided by G. Lakshmi Deepa and Madhuri Vemuri of Novartis Healthcare Private Limited.

Funding

This study was supported and funded by Novartis Pharma AG.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PRB, VG, LD, IB, TP and GD have participated in the conception and design of the study, as well as reviewed and provided inputs to the development of the manuscript, and approved the final draft of the manuscript. IB performed the statistical analyses.

Competing interests

During the past 3 years, Pierre-Régis Burgel has received honoraria for participating in advisory boards and/or lecturing from Almirall, Astra-Zeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer, and Vertex. He was the principal investigator of the current clinical study sponsored by Novartis. During the past 3 years, Thierry Perez has received honoraria for participating in advisory boards and/or lecturing from Almirall, Boehringer Ingelheim, Chiesi, GSK, Novartis, Takeda and Teva. During the past 3 years, Gaëtan Deslée has received honoraria for participating in advisory boards and/or lecturing from Astra-Zeneca, Boehringer Ingelheim, Chiesi, Novartis, and BTG/PneumRx.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was performed according to the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/83/EC and US Code of Federal Regulations Part 21), and was run according to the ethical principles of the Declaration of Helsinki. The study was approved by Comité de Protection des Personnes, Ile de France XI (Institutional ethics committee reference number# 10 064). All patients gave written, informed consent to participate in the study. The study is registered with the ClinicalTrials.gov identifier: NCT01272362.

Author details

¹Respiratory Medicine, APHP–Hôpital Cochin–Université Paris Descartes, 27 rue du Faubourg St Jacques, Sorbonne Paris Cité, Paris 75014, France.

²Respiratory Medical Department, Novartis Pharma SAS, Rueil-Malmaison, Paris, France. ³Pulmonary Department, CHU de Lille, Université de Lille, Lille, France. ⁴Respiratory Medicine, INSERM UMRS 903, Hôpital Maison Blanche–CHU de Reims, Reims, France.

Received: 3 September 2016 Accepted: 20 January 2017

Published online: 31 January 2017

References

- Seth HD, Sultan S, Gotfried MH. Role of indacaterol, a once-daily bronchodilator, in chronic obstructive pulmonary disease. *J Thorac Dis*. 2013;5(6):806–14.
- Global Strategy for the Diagnosis, Management, and Prevention of COPD, GOLD 2016.
- Boyd G, Morice AH, Pounsford JC, Siebert M, Peslis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J*. 1997;10(4):815–21.
- Cazzola M, Matera MG, Santangelo G, Vinciguerra A, Rossi F, D'Amato G. Salmeterol and formoterol in partially reversible severe chronic obstructive pulmonary disease: a dose–response study. *Respir Med*. 1995;89(5):357–62.
- Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kottakis J, Della Cioppa G, Formoterol in Chronic Obstructive Pulmonary Disease IISG. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest*. 2002;121(4):1058–69.
- Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single centre randomised, double blind, placebo controlled, crossover study. *Thorax*. 1995;50(7):750–4.
- Albert P, Agusti A, Edwards L, Tal-Singer R, Yates J, Bakke P, Celli BR, Coxson HO, Crim C, Lomas DA, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax*. 2012;67(8):701–8.
- Molimard M, Bourcereau J, Le Gros V, Bourdeix I. Total reversibility testing as indicator of the clinical efficacy of formoterol in COPD. *Respir Med*. 2005;99(6):695–702.
- Global Strategy for the Diagnosis, Management, and Prevention of COPD, GOLD 2014.
- Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, Calverley PMA, Chavannes N, Dillard T, Fahy B, Fein A, Heffner J, Lareau S, Meek P, Martinez F, McNicholas W, Muris J, Austegard E, Pauwels R, Rennard S, Rossi A, Siafakas N, Tiej B, Vestbo J, Wouters E, ZuWallack R. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23:932–946.
- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26(5):948–68.
- Pitzalis C, Jones GW, Bombardieri M, Jones SA. Ectopic lymphoid-like structures in infection, cancer and autoimmunity. *Nat Rev Immunol*. 2014;14(7):447–62.
- Kon SS, Dilaver D, Mittal M, Nolan CM, Clark AL, Canavan JL, Jones SE, Polkey MI, Man WD. The Clinical COPD Questionnaire: response to pulmonary rehabilitation and minimal clinically important difference. *Thorax*. 2014;69(9):793–8.
- Hanania NA, Sharafkhaneh A, Celli B, Decramer M, Lystig T, Kesten S, Tashkin D. Acute bronchodilator responsiveness and health outcomes in COPD patients in the UPLIFT trial. *Respir Res*. 2011;12:6.
- Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. *Chest*. 2003;123(5):1441–9.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–38.
- Calverley PMA, Albert P, Walker PP. Bronchodilator reversibility in chronic obstructive pulmonary disease: use and limitations. *The Lancet Respiratory Medicine*. 2013;1(7):564–73.
- Hanania NA, Celli BR, Donohue JF, Martin UJ. Bronchodilator reversibility in COPD. *Chest*. 2011;140(4):1055–63.
- Pellegrino R, Brusasco V. Point: Is an increase in FEV₁ and/or FVC \geq 12% of control and \geq 200 mL the best way to assess positive bronchodilator response? Yes. *Chest*. 2014;146(3):536–7.
- Hansen JE, Porszasz J. Counterpoint: Is an increase in FEV₁ and/or FVC \geq 12% of control and \geq 200 mL the best way to assess positive bronchodilator response? No. *Chest*. 2014;146(3):538–41.
- McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA, Committee TCE. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax*. 2007;62(5):411–5.
- McGarvey LP, Magder S, Burkhart D, Kesten S, Liu D, Manuel RC, Niewoehner DE. Cause-specific mortality adjudication in the UPLIFT (R) COPD trial: findings and recommendations. *Respir Med*. 2012;106(4):515–21.
- Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, Kramer B. *Inlight- study investigators*: Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur Respir J*. 2011;37(2):273–9.
- Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M, Kramer B. *Intensity study investigators*: Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *Eur Respir J*. 2011;38(4):797–803.
- Van Dijk WD, Gupta N, Tan WC, Bourbeau J. Clinical relevance of diagnosing COPD by fixed ratio or lower limit of normal: a systematic review. *Copd*. 2014;11(1):113–20.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at
www.biomedcentral.com/submit

