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Acute effects of indacaterol on lung hyperinflation in moderate COPD: A comparison with tiotropium

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KEYWORDS
Indacaterol;
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Summary
Background: Evidence has been provided that high-dose indacaterol (300 μg) can reduce lung hyperinflation in moderate-to-severe chronic obstructive pulmonary disease (COPD).
Aim: To study whether low-dose indacaterol (150 μg) also reduces lung hyperinflation in comparison with the recommended dose of tiotropium (18 μg) in moderate COPD.
Methods: This was a multicenter, randomized, blinded, 3-period cross-over, placebo-controlled study. Spirometry and lung volumes were measured before and 30, 60, 120, 180 and 240 min after the administration of single-doses of indacaterol, tiotropium, or placebo. The primary end-point was the change in peak inspiratory capacity (IC). The area under the 4-h curve (AUC_{0-4}) for IC, 1-s forced expiratory volume (FEV_1) and forced vital capacity (FVC) were secondary variables.
Results: 49 patients completed the study. On average, peak IC and AUC_{0-4} for IC were significantly greater after indacaterol than placebo by 177 mL ($p = 0.007$) and 142 mL ($p = 0.001$), respectively. Differences in peak IC and AUC_{0-4} for IC between tiotropium and placebo were 120 mL ($p = 0.07$) and 85 mL ($p = 0.052$), respectively. Differences between indacaterol and tiotropium were statistically insignificant. Peak IC increased by >20% in 12 patients with indacaterol and 9 with tiotropium ($p = 0.001$), and by >30% in 8 patients with indacaterol

Abbreviations: COPD, chronic obstructive pulmonary disease; LABA, long-acting beta-agonist.

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and 3 with tiotropium ($p = 0.001$). The effects of indacaterol and tiotropium on FEV_1 and FVC were statistically significant vs placebo.
Conclusions: Low-dose indacaterol has a bronchodilator effect that is similar to the recommended dose of tiotropium, but it is slightly superior in reducing lung hyperinflation.
Trial registration: ClinicalTrials.gov number: NCT00999908.

Introduction

Long-acting bronchodilators are central to the management of chronic obstructive pulmonary disease (COPD).[1,2] Several clinical trials have shown that sustained bronchodilatation is associated with improvements in the so-called patient-centered outcomes, namely, symptoms, exacerbations, exercise tolerance and health status. These effects were obtained with either long-acting β_2-agonists (LABA)[3–6] or the muscarinic antagonist, tiotropium.[7–9] However, when directly compared with LABA, tiotropium showed some superiority,[9] which was attributed to its longer duration of action, i.e., 24 vs 12 h.

Indacaterol is a new LABA with a 24-h bronchodilator effect (Ultra-LABA), which proved to be superior to both formoterol and salmeterol based on measurements of 1-s forced expiratory volume (FEV_1).[10–13] However, FEV_1 is poorly correlated with symptoms and exercise intolerance,[14–15] which is more likely determined by dynamic pulmonary hyperinflation in COPD.[16–18] Indeed, a reduction of pulmonary hyperinflation, as reflected by an increase in inspiratory capacity (IC), has been shown to occur in moderate-to-severe COPD patients treated with either salmeterol[19] or tiotropium,[20,21] and this was consistently associated with a reduction in dyspnea and an increase in exercise tolerance. In a recent study, Beier and colleagues[22] found that high-dose indacaterol (300 μg) caused a significantly larger increase in IC than the recommended dose of formoterol.

The present study was designed to investigate whether the lower available dose of indacaterol (150 μg) can also reduce pulmonary hyperinflation in comparison with either placebo or the recommended dose of tiotropium (18 μg), the other available once-daily bronchodilator, in patients with moderate COPD.

Methods

The study protocol was approved by the Ethics Authority of each participating center. Written informed consent was obtained from each patient before entering the study.

Patient characteristics

All patients were at least 40 years old with a $\geq$ 10 pack-year smoking history. They were required to have a clinical diagnosis of COPD confirmed by post-bronchodilator (salbutamol 4 × 100 μg) $FEV_1/FVC < 0.7$[1] and FEV_1/VC below the lower limit of normality.[23] Based on FEV_1, they had to be classified as moderate, i.e., GOLD stage II.[1] Patients were not included if they had a history of asthma or other allergic diseases, an elevated blood eosinophil count, or a recent respiratory tract infection.

Study design

This was a multicenter, randomized, single blinded, single dose, 3-period cross-over (Latin-square design), placebo-controlled study. Seven Pulmonary Units from University/General Hospitals participated in the study by recruiting patients from their outpatient clinics. At the first visit, patients were screened for eligibility to take part in the study. Those who met the inclusion criteria were asked to suspend any regular treatment with long-acting bronchodilators (tiotropium or LABA) and inhaled corticosteroids for the duration of the study. Inhaled salbutamol was allowed as rescue medication on demand (up to a maximum of 8 puffs/day). After seven days, patients had a second screening visit to assess whether they still met the inclusion criteria and were still willing to participate in the study. Those who were still eligible to take part in the study were randomized to receive single-doses of indacaterol (150 μg), tiotropium (18 μg) or placebo on three occasions, separated by 5-day washout periods. All doses were inhaled between 08:00 and 10:00 h, a.m.

On each study day, lung volumes and spirometry were measured before and again 30, 60, 120, 180 and 240 min after the administration of trial treatments. Investigator staff and persons performing assessments and data analysis remained blind to the treatment sequence from the time of randomization until database lock. Study drugs were received by a designated person at each study site and kept in a secured location to which only the designated unblinded site personnel had access.

Lung function measurements

Lung volumes were measured by a constant-volume variable-pressure body plethysmograph according to ATS/ERS recommendations.[24] After a few regular tidal breaths, functional residual capacity (FRC) was measured by having the patient panting against a closed shutter at a frequency slightly <1 Hz. After the opening of the shutter and a few quiet tidal breaths without disconnecting from the mouthpiece, the patient fully inspired to total lung capacity (TLC) and IC was measured as the difference between TLC and FRC. Measurements were taken in triplicate and the average values of FRC and IC retained for analysis. Residual volume was calculated as the difference between TLC and the largest slow vital capacity (VC) from three acceptable maneuvers. Forced expiratory maneuvers were then

obtained and analyzed according to the ATS/ERS recommendations.[25] The largest FEV_1 and FVC from three acceptable and repeatable maneuvers were taken, even if they were not from the same curve.

Statistical analysis

The primary efficacy variable was the peak increase in IC from pre-dose among the readings at 30, 60, 120, 180, 240 min post dose, and was summarized by sequence and treatment for the per-protocol population. We calculate an IC peak clinical difference of 65 ml with 80% power, assuming a standard deviation of 170 ml, with a one-tailed 0.025 level of significance. Secondary variables were the normalized area under the 4-h curve (AUC_{0-4}) for IC, FEV_1 and FVC, and the number of patients with peak IC increments exceeding predetermined thresholds, i.e., 10%, 20% and 30%. Statistical significance was tested by analysis of variance (ANOVA) with the following factors: treatment, period, sequence and patient-within-sequence. Least square means and associated standard errors were calculated for each treatment group as well as treatment differences with 95% confidence intervals. Mc Nemar test was used for categorical data. $P < 0.05$ was considered statistically significant.

Results

Fifty-four out of 62 patients screened were randomized and 49 of them completed the study. The five withdrawals were due to protocol violations (Fig. 1).

Their demographic and functional characteristics are shown in Table 1.

Table 1 Patient characteristics.

Age (yr)	69 ± 9
Sex (male/female)	45/4
Smoking habit (current/former)	13/36
BMI (Kg/m^2)	27.4 ± 4.6
VC (L)	3.18 ± 0.71
IC (L)	2.33 ± 0.54
FVC (L)	3.11 ± 0.69
FEV_1 (L)	1.81 ± 0.40
FEV_1 (% of predicted)	68.7 ± 9.7
FEV_1/FVC (%)	58.2 ± 7.7
FRC (L)	4.97 ± 1.16
FRC (% of predicted)	147.5 ± 33.6
TLC (L)	7.32 ± 1.52
TLC (% of predicted)	114.4 ± 19.2
RV (L)	3.67 ± 1.10
RV (% of predicted)	158.4 ± 40.5

Data are ± SD unless otherwise stated. All lung function data are post-bronchodilator.

34 patients had TLC>100% predicted; 43 patients had FRC>110% predicted and 37 patients had RV>120% predicted. No significant difference was observed among baseline values for any of the variables considered in the study and treatment sequences. Before the study, 18% of patients were not assuming any regular pharmacotherapy; 38% of them were on fixed dose LABA + ICS combinations; 33% were on tiotropium, and 11% were on LABA monotherapy.

Compared with placebo, the mean increments of peak IC (Fig. 2) and AUC $_{0-4}$ for IC (Fig. 3) were significantly larger

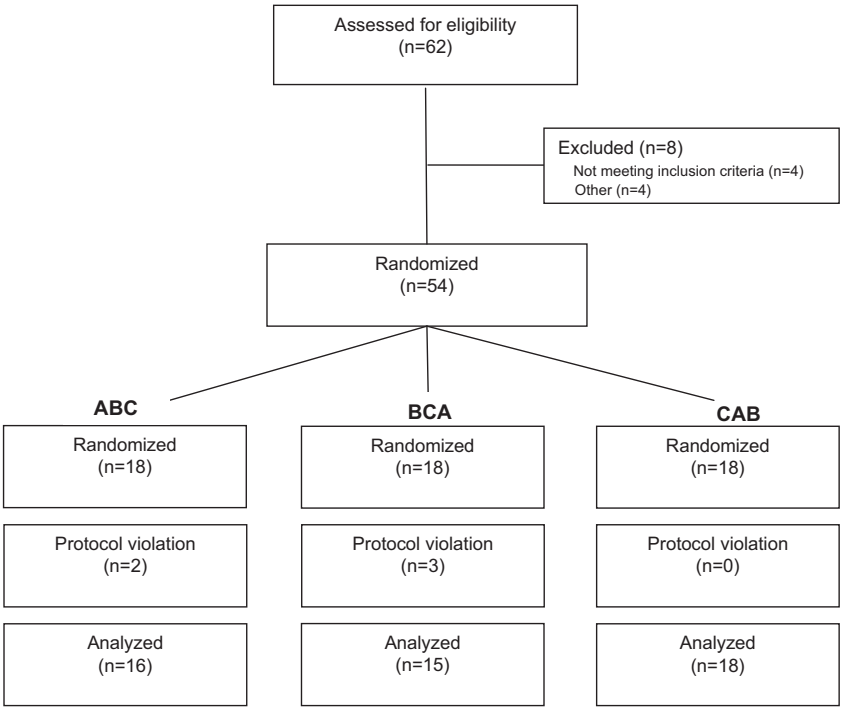

Figure 1 Study design and patient disposition of the 3-period cross-over sequences. A: indacaterol; B: tiotropium, C: placebo.

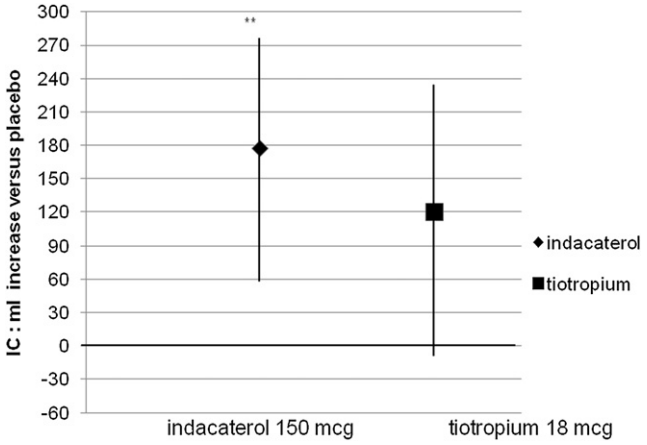

Figure 2 Difference in peak inspiratory capacity (IC). Data are mean ± 95% CI. $^{**}p < 0.01$ versus placebo.

with indacaterol (by 177 mL, $p = 0.007$ and 142 mL, $p = 0.001$, respectively). With tiotropium the mean increments of peak IC and AUC $_{0-4}$ for IC tended to be larger than after placebo without reaching the predetermined level of statistical significance (by 120 mL, $p = 0.07$ and 85 mL, $p = 0.052$, respectively). Differences between indacaterol and tiotropium in peak IC and $AUC_{0.4}$ for IC were not statistically significant ($p = 0.18$ and $p = 0.38$, respectively).

The distribution of percent changes in peak IC from baseline with indacaterol or tiotropium is shown in Fig. 4. Peak IC increased by >10% in 27 patients with indacaterol and 29 with tiotropium ($p = 0.06$), by >20% in 12 patients with indacaterol and 9 with tiotropium ($p = 0.001$) and by >30% in 8 patients with indacaterol and 3 with tiotropium ($p = 0.001$).

Both indacaterol and tiotropium increased the AUC_{0-4} of FEV_1 and FVC (Fig. 5) significantly compared with placebo ($p < 0.01$), without significant differences between them.

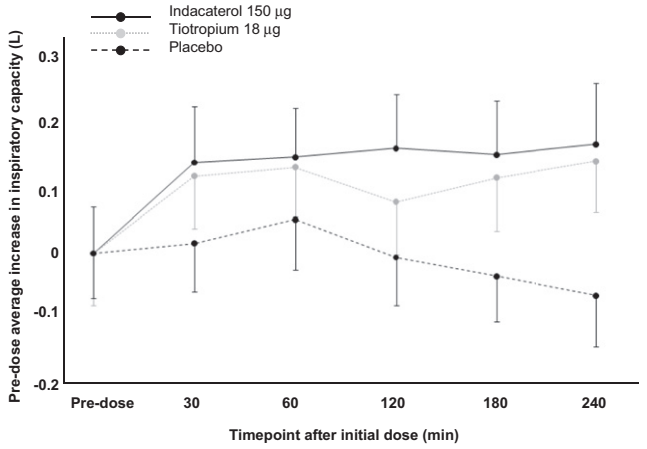

Figure 3 Changes in inspiratory capacity (IC) from pre-dose over 4 h after a single dose of indacaterol, tiotropium or placebo. Data are mean ± SE. Statistical differences in AUC_{0-4}: $^{**}p < 0.05$ versus placebo; $\#\#p < 0.05$ versus placebo.

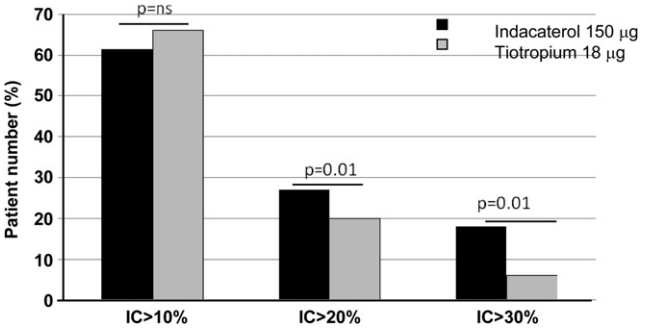

Figure 4 Distribution of patients with significant improvements in inspiratory capacity (IC) over 4 h. *P*-values denote significant differences between indacaterol and tiotropium.

The mean changes of FRC, RV, and TLC, at the 4th hour after administration, are illustrated in Fig. 6.

Discussion

The main findings of this study are that: 1) 150 µg of indacaterol significantly increased IC in patients with

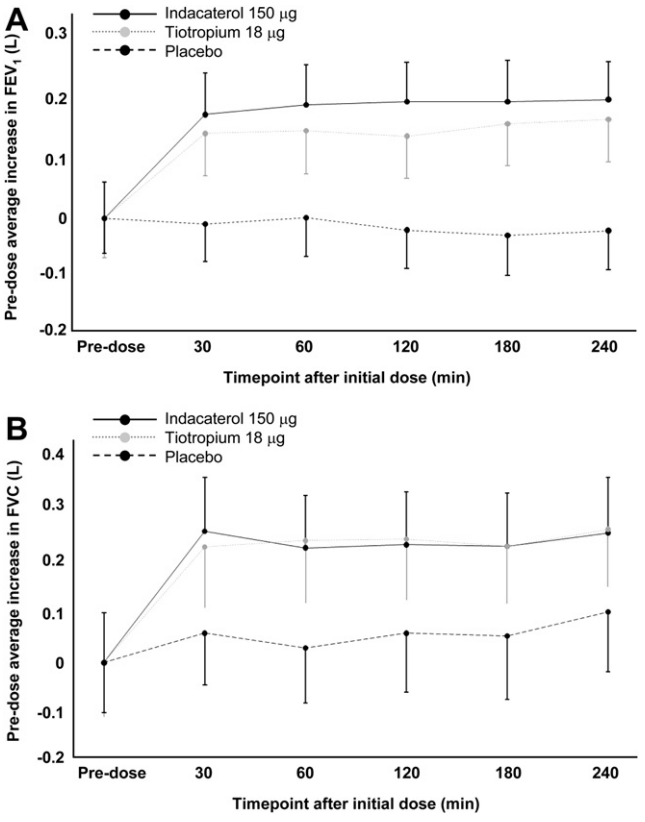

Figure 5 Changes in FEV_1 AUC $_{(0-4)}$ and FVC AUC $_{(0-4)}$ from pre-dose over 4 h after a single dose of indacaterol, tiotropium or placebo. A, Indacaterol vs placebo $p < 0.02$, tiotropium vs placebo: $p < 0.02$, indacaterol vs tiotropium: $p = 0.6$. B, Indacaterol vs placebo $p < 0.02$, tiotropium vs placebo: $p < 0.02$, indacaterol vs tiotropium $p = 0.4$. Data are expressed as mean ± SE; Differences between treatments were for all time-points.

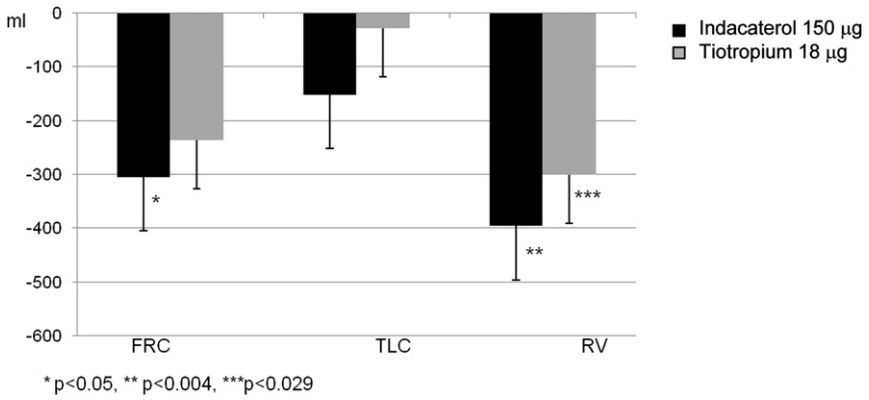

Figure 6 Changes in FRC, TLC and RV at the 4th hours after administration.FRC was decreased compared to pre-dose by 305 ± 100 ml with indacaterol ($p = 0.01$) and by 236 ± 88 ml with tiotropium ($p = 0.053$); TCL by 152 ± 0.114 ml with indacaterol ($p = 0.208$) and by 28 ± 85 ml with tiotropium.($p = 0.806$); RV by 396 ± 0.125 ml with indacaterol ($p = 0.004$) and by 301 ± 0.106 ml with tiotropium ($p = 0.029$) Data are expressed as mean ± SE.

moderate COPD on the first day of administration and 2) this effect was slightly superior to that of the recommended dose of tiotropium, despite similar effects on FEV_1 and FVC.

In patients with COPD, dynamic pulmonary hyperinflation is often present at rest.[26] Since RV and FRC are generally increased to a greater extent than TLC, the inspiratory reserve available for increasing tidal volume is reduced, which is considered to be a major mechanism for reduced exercise tolerance in these patients. Breathing at high lung volumes is associated with a remarkable increase in the elastic work of breathing due not only to the greater lung recoil, but also to the need of counterbalancing the inward recoil of the chest wall. In fact, dyspnea, exercise tolerance and health status are loosely correlated with FEV_1, which is the most popular index of airway caliber, but better correlated with IC, which reflects lung hyperinflation.[27–29] Therefore, it is desirable that measurements of lung volumes are included when the effects of bronchodilators are to be assessed in COPD.[30,31]

In the present study we observed the effect of indacaterol and tiotropium during the first 4 h on the first day of administration because both drugs resulted in peak effect at 1.5—2 h with a mean FEV_1 improvement. The lower available dose of indacaterol (150 μg) caused increments of both FVC and FEV_1 that were not significantly different from those caused by the recommended dose of tiotropium (18 μg). Although both peak IC and AUC_{0-4} for IC were greater after either indacaterol or tiotropium than after placebo, these differences reached statistical significance only with indacaterol.

Previous studies have shown that IC has a within-session natural variability that is about 9% or 220 mL.[25,32] Therefore, we considered patients with an increase in IC>10% as volume responders to bronchodilators. While no significant difference was observed between indacaterol and tiotropium in the number of patients who showed a >10% increase in IC, the number of patients with a larger (>20% and >30%) improvement in IC was significantly greater with indacaterol than tiotropium.

These results are unlikely to be due to differences in baseline values, because there were no differences in baseline lung function between treatment sequences. Furthermore, our results cannot be due to differences in the doses of the drugs, because the effects on FEV_1 and FVC were not significantly different.

There is a solid evidence showing potent bronchodilator efficacy of indacaterol in COPD.[10–13] Beier and colleagues[22] have also shown that 300 μg indacaterol had a significantly greater effect than formoterol on both FEV_1 and IC. The present study is the first one directly comparing the effects of low-dose indacaterol with the marketed dose of tiotropium on lung hyperinflation. The decrease in RV, and FRC appeared to be greater with indacaterol than with tiotropium.

The majority of studies on indacaterol to date recruited patients with moderate-to-severe COPD, i.e., with FEV_1 <80% and >30% of the predicted value. The present study was designed to include only patients with moderate COPD, i.e., with FEV_1 <80% and ≥50% of the predicted value. A recent longitudinal study has shown that in this severity group tiotropium may improve lung function and slightly but significantly decrease the rate of decline of FEV_1 over a 4-year period.[33] Therefore, patients with moderate COPD are likely to experience substantial benefit from regular therapy with long-acting bronchodilators.

A potential limitation may be that this study only examined acute effects. By not examining effects of the study drugs beyond a single day we might have underestimated the potential acute effect of both drugs because of the delay in the achievement of a pharmacodynamic steady state for these drugs. In addition we have only examined the acute effects of the study drugs over the first 4 h. Hence we do not know whether the comparison might have yielded the same results over the entire 24 h duration of action.

We must mention that a previous study which compared the acute effect of tiotropium versus a combination therapy with single inhaler budesonide/formoterol on the degree of resting pulmonary hyperinflation documented that tiotropium is able to modify IC even after an acute administration points out its capacity of influencing expiratory flow limitation in a very fast manner.[34] In a 12-week study published recently, Buhl et al[35] showed that

indacaterol 150 mcg and tiotropium 18 mcg had similar effects on trough FEV_1 but indacaterol was superior in reducing dyspnea.

The results of the present study are encouraging for the designing of longer and more complex studies. In this regard, it is worth noting that even patients with mild COPD (i.e., FEV_1 >80% of the predicted value) have a reduced exercise tolerance[36] which can be improved by bronchodilatation.[37] It has been suggested that patients with COPD might receive additional benefit from regular treatment with long-acting bronchodilators earlier in the course of their diseases than was traditionally thought, and that both airflow obstruction and lung hyperinflation should therefore be targeted.[38] Data from our study and those by Beier and colleagues[22] show that indacaterol is effective in improving spirometry and decreasing pulmonary hyperinflation on the first day of administration. Whether this rapid functional improvement may influence patient compliance to the treatment and patient-centered outcomes remains to be established in long-term studies.[39,40]

The data of the present study also demonstrates that IC may be a more sensitive measure than FEV_1 in discriminating between the effects of indacaterol and tiotropium on lung function in patients with moderate COPD.

Conclusion

In summary, this study shows that the lower available dose of the new ultra-long-acting bronchodilator, indacaterol, acutely improved spirometry in a manner similar to the recommended dose of tiotropium, but it was slightly superior in reducing lung hyperinflation. Long-term studies are necessary to evaluate whether this difference translates into greater beneficial effects on clinical end-points such as exercise tolerance and dyspnea.

Author contributions

AR, SC, MC and VB conceived the study, participated in its design, in its implementation and in data interpretation. IC, CG and AF participated in study implementation and in data interpretation. All authors were involved in drafting the manuscript and have read and approved the final manuscript.

Conflict of interest statement

A. Rossi: received honoraria for speaking and consulting and/or financial support for attending meetings from AstraZeneca, Boeheringer Ingelheim, Chiesi Farmaceutici, Novartis, Nycomed and Pfizer.

S. Centanni: received honoraria for speaking and consulting and/or financial support for attending meetings from Boeheringer Ingelheim, Chiesi Farmaceutici, Novartis and Pfizer.

I. Cerveri: received honoraria for speaking and consulting and/or financial support for attending meetings from Boeheringer Ingelheim, Glaxo-Smith-Kline, Novartis and Pfizer.

C. Gulotta: received honoraria for speaking and consulting and/or financial support for attending meetings from Boeheringer Ingelheim, Novartis and Pfizer.

A. Foresi: received honoraria for speaking and consulting and/or financial support for attending meetings from AstraZeneca, Boeheringer Ingelheim, Chiesi Farmaceutici, Menarini, Novartis and Pfizer.

M. Cazzola: received honoraria for speaking and consulting and/or financial support for attending meetings from AstraZeneca, Boeheringer Ingelheim, Chiesi Farmaceutici, Day, GSK, Menarini Farmaceutici, Mundipharma, Novartis, Nycomed, Pfizer and Sigma-Tau.

V. Brusasco: received honoraria for speaking and consulting from Boeheringer Ingelheim, Chiesi Farmaceutici, Dompé, Novartis, GSK, Novartis and Nycomed.

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