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Comparative Tolerability of a Long Acting β2 Agonist-Indacaterol Verses a Long Acting Muscarinic Antagonist-Tiotropium for the Treatment of COPD Patients

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ABSTRACT

Background: An open label, comparative study to evaluate the tolerability of a long acting β2 agonist- indacterol with a long acting muscuranic antagonist-tiotropium for the treatment of COPD, was carried out in the OPD and IPD of HIMSR and associated HAHC Hospital, Jamia Hamdard, New Delhi. **Methods:** The total number of 51 patients (only 44 patients completed the study) were enrolled for the study they comes under moderate to severe COPD, over the age of 40 years, for a period of 4 months. The patients received either 150 µg or 300 µg indacterol or l8 µg of tiotropium as single dry powder inhaler. The patients were screened for SGRQ-C scores and adverse events at baseline and then after first, fourth and eighth weeks of treatment. **Results & Conclusion:** The total SGRQ-C scores of indacaterol 300/150 µg indicated significant improvement in quality of life during 8 weeks of treatment. Indacaterol 300 µg was found to be significantly better than tiotropium 18 µg in improving health status in terms of symptoms, activity and impact component. Indacaterol 150 µg was also found to be statistically superior to tiotropium 18 µg in terms of improving symptoms, activity, impact and total SGRQ-C scores but the impact component of SGRQ-C score was affected to a lesser extent. Both indacterol and tiotropium were found to be well tolerated and safe during study period.

Keywords: Indacaterol, tiotropium, COPD

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is estimated to affect 10% of the world's population aged more than 40 years. The prevalence is expected to continue to increase over coming years.[1,2] The prevalence of COPD is appreciably higher in smokers and ex-smokers than in nonsmokers, in those over 40 years of age than those under 40, and in men than in women.[3] Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.[4] COPD kills more than 3 million people every year, making it the 4th largest cause of death in the world.[5] It has been estimated that by the year 2030, COPD will become the third biggest cause of death. According to the World Health Organization, COPD kills more people than HIV-AIDS, Malaria and Tuberculosis all put together in the South East Asian region. The mortality rates due to COPD are anticipated to increase by over 160% over the next 2 decades.[6] Half a million people die every year due to COPD in India, which is over 4 times the number of people who die due to COPD in USA and Europe.[7] Treatment of COPD is now aimed at immediately relieving and reducing the impact of symptoms, as well as reducing the risk of future adverse health events such as exacerbations. Appropriate pharmacological therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.[8,9]

Bronchodilators are central to symptom management in COPD as they increase the FEV1 or change other spirometric variables. These medications improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise.[10-12]

The long-acting anticholinergic tiotropium (LAMA) has a pharmacokinetic selectivity for the M3 and M1 receptors and has duration of action of more than 24 hours.[13-17] Tiotropium reduces exacerbations and related hospitalizations, improves symptoms and health status,[18] and improves the effectiveness of pulmonary rehabilitation.[19] In a large trial, tiotropium was superior to salmeterol in reducing

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exacerbations although the difference was small.[20,21] In another large, long-term clinical trial on patients with COPD, there was no effect of tiotropium added to other standard therapies on the rate of lung function decline and no evidence of cardiovascular risk.[22]

Indacaterol is a once daily long acting beta2-agonist, with duration of action of 24 hours.[23,24] It is being increasingly used for long term symptomatic control of COPD patients. It has proved to be superior to both formoterol and salmeterol based on measurements of FEV1.[23,25,26] In previous clinical studies, indacaterol has demonstrated good overall safety and tolerability profile.[27-29] The present study was conducted to evaluate the comparative tolerability of indacaterol with tiotropium in patients of COPD.

MATERIALS AND METHODS

Selection of Patients

All patients aged ≥ 40 years and a smoking history of at least ≥ 10 pack-years (current or past smokers), with clinical diagnosis of COPD confirmed by post-bronchodilator (salbutamol 4 × 100 mcg) FEV1/FVC < 0.7, and moderate to severe COPD (stage II/III) as per the GOLD guidelines were included in the study. Patients with a history of asthma or other allergic diseases (seasonal or perennial allergic rhinitis), an elevated blood eosinophil count (>400/mm3), recent respiratory tract infection, significant unstable cardiovascular or metabolic co-morbidity and history of hypersensitivity to LAMA or LABA were excluded.

Study site

Patients visiting Medicine Out Patient Department (OPD) and In Patient Department (IPD) of Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi, were screened and included in the present study.

Study Design

The study was an open label, comparative study to evaluate the tolerability of a long acting β2 agonist-indacaterol with a long acting muscarinic antagonist-tiotropium in patients of COPD.

At the first visit, patients were screened for eligibility criteria to take part in the study. Those who met the inclusion criteria were asked to suspend any regular treatment with long acting bronchodilators and inhaled corticosteroids, or short acting anticholinergics for a wash out period of 7 days. Inhaled salbutamol was allowed as a rescue medication on demand (up to a maximum of 8 puffs per day). The patients' demographics were recorded. After a 7 days wash out period, patients had a second screening visit to assess whether they still met the inclusion criteria and were willing to participate in the study. The patients then received either indacaterol 150/300 µg or tiotropium18 µg once daily as single dry powder inhaler (DPI) for eight weeks. The patients were screened for St George's Respiratory Questionnaire for COPD (SGRQ-C) scores and adverse events at base line and then at first, fourth and eighth week of treatment.

Assessments

COPD control questionnaire (SGRQ-C)

St George's Respiratory Questionnaire for COPD (Pre dose and Post dose intervals) was used to assess the symptoms, activity and impact component of patients. The total SGRQ-C score was calculated for each patient.

Adverse Event / ADR Monitoring (All adverse events during the study period were recorded)

Laboratory tests viz. measurement of blood glucose and serum potassium concentration; vital signs (blood pressure and pulse rate) and ECG were recorded.

Naranjo's Probability Scale for ADR was used.

Ethical Considerations

The Protocol and the corresponding Informed Consent Form (ICF) were submitted to the Institutional Review Board (IRB), Jamia Hamdard for the approval to conduct this study.

The study was commenced only after due approval by IRB.

Informed Consent Form

An oral and written consent was obtained from patients before the participation of the subjects in the study.

Statistical Analysis

The data is expressed as mean, SD, SEM and 95% C.I. For assessing the tolerability of a drug at different time interval (0-8 weeks), repeated measures ANOVA followed by Tukey test was performed. For comparing the difference between treatments groups, one way ANOVA was performed followed by Tukey Kramer test for multiple comparisons. $P < 0.05$ was considered statistically significant. The data was analysed using graph pad instat.

RESULTS

A total of 51 patients with moderate to severe COPD were enrolled in this study but only 44 patients could be studied till the end of eighth week of treatment, since 7 patients were lost to follow up. The study comprised of 44 patients, out of which 36 were males and 8 were females, 27 were current smokers and 17 were ex-smokers. Out of 44 patients 15 patients (34%) received indacaterol 150 µg, 13 patients (30%) received indacaterol 300 µg and 16 patients (36%) received tiotorpium 18 µg as DPI once a day. The Patients' demographics and SGRQ-

C scores were taken at baseline (Table 1). The Patients were then assessed for SGRQ-C scores and adverse events after first, fourth and eighth week of treatment. The symptoms, activity and impact as well as total scores were similar in each treatment group at baseline.

Indacaterol 150 µg, given once a day, decreased (improved) mean SGRQ-C scores in terms of symptoms from 259.26 to 184.46 (28.85%), activity from 339.86 to 227.20 (33.13%) and impact component from 708.40 to 585.86 (17.29%) as well as total SGRQ-C Scores from 1307.53 to 997.53 (23.7%) after 8 weeks of treatment. Similarly indacaterol 300 µg, given once a day, decreased (improved) mean symptoms from 259.30 to 183.23 (27.02%), mean activity from 353.46 to 233.69 (33.88%) and impact component from 706.61 to 558.38 (20.97%) as well as total SGRQ-C scores from 1319.38 to 975.30 (26.07%) after 8 weeks of treatment. Tiotropium 18 µg, given once a day, decreased (improved) mean symptoms from 264.87 to 237.56 (10.31%), activity from 336.18 to 282.23 (19.94%) and impact components from 706.81 to 641.75 (9.20%) as well as total SGRQ-C Scores from 1307.87 to 1161.56 (11.19%) after 8 weeks of treatment. Although the SGRQ-C scores decreased (improved) significantly in all treatment groups when compared with baseline ($p < 0.001$), indacaterol 300 µg was found to be statistically superior to tiotropium 18 µg in terms of improving symptoms, activity and impact as well as total SGRQ-C Scores ($p<0.001$). Indacaterol 150 µg was also found to be statistically superior to tiotropium 18 µg in terms of improving symptoms, activity and total SGRQ-C Scores ($p<0.001$) but not in the impact component. However, the SGRQ-C total scores were found to be similar between indacaterol 150 µg and indacaterol 300 µg (Table 2).

Table 1: Subject Demographics and Baseline Characteristics

Characteristics ↓	Indacaterol 150 µg	Indacaterol 300 µg	Tiotropium 18 µg
No of Patients (n) 44	15	13	16
Age, yrs., mean (SD)	60.4 (8.68)	60.2 (9.34)	61.7 (9.63)
Sex (male/female)	12 / 3	11 / 2	13 / 3
Smoking habit (current/ex-smoker)	9 / 6	8 / 5	10 / 6
Symptoms component, mean (SD)	259.20 (54)	259.30 (58.76)	264.87 (54.16)
Activity component, mean (SD)	339 (93)	353.46 (95.65)	336.18 (91.45)
Impacts component, mean (SD)	708 (111)	706.61 (113.58)	706.81 (109.63)
Total score (SGRQ-C) mean (SD)	1307 (152)	1319.38 (160.06)	1307.87 (147.87)

Table 2. Changes in SGRQ-C scores (symptoms, activity, impacts & total score) from base line to 8 weeks in Indacaterol 150 µg / 300 µg and Tiotropium 18 µg

Treatment Group	SGRQ-C scores	At base line				At 8th week				Difference			
		Symptom	Activity	Impact	Total score	Symptom	Activity	Impact	Total score	Symptom	Activity	Impact	Total score
Indacaterol 150 µg (Group I) n = 15	Mean	259.26	339.86	708.4	1307.53	184.46	227.2	585.86	997.53	-74.80***,b	-112.66***, b	-122.53**, b	-310.00***, b
	SD	54.86	93.42	111.87	152.82	44.43	69.34	150.48	151.71	17.9	33.57	76.48	94.49
Indacaterol 300 µg (Group II) n = 13	Mean	259.3	353.46	706.61	1318.38	183.23	233.69	558.38	975.30	-76.07***, b	-119.76***, b	-148.23***, b	-344.07***, b
	SD	58.76	95.65	113.58	160.06	45.83	70.42	110.56	136.96	19.25	34.8	14.9	44.04
Tiotropium 18 µg (Group III) n = 16	Mean	264.87	336.18	706.81	1307.87	237.56	282.25	641.75	1161.56	-27.31c	-67.06c	-65.06c	-146.31c
	SD	54.16	91.45	109.63	147.87	53.89	93.51	108.45	148.80	3.62	27.58	5.84	8.85

** $p < 0.01$ (indacaterol 150 µg vs tiotropium 18 µg),
*** $p < 0.001$ (indacaterol 300 µg vs tiotropium 18 µg)
[b] $p < 0.001$ when compared with base line,
[c] $p < 0.01$ when compared with base line.

The laboratory investigations viz. blood glucose, serum potassium and vital signs such as pulse rate, blood pressure and ECG were performed during the period of baseline, four weeks and eight week of drug treatments. There were no significant changes in blood glucose, serum potassium or blood pressure and pulse rate during the treatment with indacaterol 150/300 µg or tiotropium 18 µg. ECG was also

within normal limit (WNL). Only three patients reported dry mouth with tiotropium and two patents reported cough after receiving indacaterol 150/300 µg from each group respectively.

DISCUSSION

The objective of the study was to compare the tolerability (In terms of symptoms, activity and impact components as well as adverse event or ADR) of long acting β2 agonist-Indacaterol with long acting muscarinic antagonist-Tiotropium in patients with COPD on the basis of SGRQ-C scores and adverse drug monitoring. SGRQ-C is designed to measure health impairment in terms of symptoms, activity and impact scores.

Our findings for indacaterol 150/300 µg are in agreement with those of Donohue et al., 2010, who reported that once- daily indacaterol was as effective as once-daily tiotropium in improving clinical outcomes for patients with COPD.[23] The SGRQ-C scores in our study were also significantly decreased (improved) for indacaterol 150/ 300 µg as well as tiotropium 18 µg. Though Donohue et al., found a significant decrease in total SGRQ-C scores for indacaterol 150/300 µg at 26 weeks, the corresponding results for tiotropium were not significant. In our 150/300 study both the doses of indacaterol were found to be significantly superior to tiotropium in improving SGRQ-C scores in terms of symptoms, activity, impact components as well as total scores.

We found no major adverse effect with either 150/300 µg indacaterol or tiotropium 18 µg. There were no significant changes in blood glucose, serum potassium, blood pressure or pulse rate in any of the treatment groups when measured at one month and two months from baseline. The ECGs of the 28 patients were also found to be within normal limits. The only minor side effects observed were dry mouth in 18% patients receiving tiotropium and cough in 7% patients receiving indacaterol. This compare well with the study by Chapman et al., 2011 who reported that indacaterol had no clinically significant effects on ECG findings, or on serum potassium or plasma glucose levels and was well tolerated during one year of treatment.[31]

CONCLUSION

- Treatment with both once-daily Indacaterol and Tiotropium were effective in improving health status in patients with moderate to severe COPD as assessed by SGRQ-C scores.
- Indacaterol 150/300 µg were found to be significantly superior to tiotropium 18 µg in improving health status in terms of symptoms, activity and impact components, as well as total SGRQ-C scores and provided significant improvement in quality of life during eight weeks of treatment.
- Both indacaterol and tiotropium were found to be well tolerated and safe during the study period.

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