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Original Article

Efficacy and Safety of Inhaled Indacaterol and Tiotropium in Patients of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death worldwide. Indacaterol is a new once daily inhaled bronchodilator, recently approved for the treatment of COPD. Once daily dosing is an important step to improve the adherence and compliance of the patients. **Methods:** Efficacy and Safety of Indacaterol and Tiotropium in Patients of COPD with Stage-2 and Stage-3 GOLD criteria were compared. Total 119 patients were divided into Indacaterol group and Tiotropium group receiving 150 mcg daily of Indacaterol and 18 mcg daily of Tiotropium in each group respectively. Efficacy treatment was determined by assessment of Pulmonary function test (PFT), Symptom score and SGRQ (St. George's Respiratory Questionnaires) score at day zero (before therapeutic intervention) and at two weeks of interval till 24 weeks. **Results:** The treatment with inhaled indacaterol 150 mcg once daily and inhaled tiotropium 18 mcg once daily improved spirometric variable, FEV1, decrease in mean Symptoms score and in mean SGRQ in Grade-2 and Grade-3 COPD patients. **Conclusion:** Indacaterol (150 mcg/day) is non-inferior to tiotropium (18 mcg /day) in efficacy and safety profile of Grade-2 and Grade-3 patients with COPD.

Key words: COPD, FEV1, GOLD, SGRQ, Symptom score.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation (GOLD 2019). It is the major cause of chronic morbidity and mortality throughout the world. COPD is estimated to affect 10% of the world's population aged ≥40 years and prevalence may increase in coming years.[1] It is projected to be the 3rd leading cause of death by 2020. Mahesh *et al.* in 2009 reported higher prevalence of COPD (7.1%) in adults 40 years and above.[2] A recent systematic review (2012) reported the prevalence rates of COPD in adults up to 9.9% in urban India.[3]

Long-acting inhaled bronchodilators are usually recommended in managing the symptoms of patients of COPD.[4] These agents are either β2-agonists administered twice daily (formoterol/salmeterol) or the once-daily anticholinergic (tiotropium).

Indacaterol is a new inhaled ultra-long-acting β2 agonist with duration of action of 24 hr and administered once daily.[5] The prolonged duration of bronchodilation has resulted in reduced dosing frequency and better patients' adherence and compliance.[6] It has been recently approved in the India at two doses, 150 μg and 300 μg once daily for maintenance and treatment of patients with COPD.[7] The efficacy and safety of inhaled indacaterol in GOLD stage-2 patients of COPD have also been recently shown.[8]

The studies available for comparing the efficacy and safety of indacaterol with other long acting bronchodilators in the different parts of world are limited. Hence it was considered worthwhile to design the comparative study of indacaterol and tiotropium in patients of COPD in doses of 150 mcg/day and 18mcg/day respectively.

METHOD

The study was conducted in Department of Pharmacology and Department of Tuberculosis and Respiratory diseases of J.N. Medical College and Hospital, A.M.U, Aligarh, India from April 2014 to October 2015 on the patients of COPD. The ethical clearance was approved by Institutional Ethics Committee (IES) of J.N. Medical College and Hospital A.M.U Aligarh and the study was also registered with Clinical Trials Registry-India (ctri/2015/01/005430). Informed and written consent of all patients was taken before enrolling them in the study.

Study design

This was a randomized, prospective, open label and parallel group study. Eligible patients were randomized into two groups in a ratio of 1:1 according to the table generated by random allocation software. Indacaterol group patients were administered with indacaterol 150 mcg in the form of dry powder inhaler once a day in the morning and tiotropium group was administered with tiotropium 18 mcg in the form of dry powder inhaler (DPI) once a day in the morning.

Inclusion criteria

Patients having age more than 18 years of Grade II and III COPD as *per GOLD guidelines* were included in study.

Efficacy Assessments: Efficacy was determined by assessment of pulmonary function test (PFT), Symptom score[9] and SGRQ (St. George's Respiratory Questionnaires) score.[10]

FEV_1 and Ratio of FEV1/FVC were recorded at day zero (before therapeutic intervention) and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 weeks after drug treatment. PFT was done by SPIROLAB II of Department of TB and Respiratory Diseases, JNMC, AMU, Aligarh.

Individual spirograms were checked for acceptability and reproducibility. After three acceptable spirograms were taken, the best values of FEV1 and ratio of FEV1/FVC were noted down.

The complaints of patients were assessed by symptom score. Symptom score included major complaints of COPD i.e. (1) shortness of breath, (2) cough (3) chest tightness (4) night time awakening. For example, the Shortness of breath is graded as follows: None (unaware of any difficulty), mild, moderate, marked and severe (almost constant, present even when resting). Health status was assessed by St. George's Respiratory Questionnaires.

Safety assessment

All adverse events experienced by a patient or observed by the investigator were recorded at each visit. Adverse drug reactions were assessed on Naranjos' ADR Probability Scale and onset and severity classification. Additional laboratory safety tests were performed wherever required.

Statistical analysis

The data of the two groups were compared and analyzed by using SPSS software (version-20). For intra-group comparison paired *t*-test and for intergroup comparison unpaired *t*-test was used. Fisher's exact test is used for comparison of adverse events in both the groups.

RESULTS

A total of 145 patients were enrolled, out of which 26 patients were excluded from the study (failed to report on subsequent visits, shifted to other drugs, developed severe exacerbations of COPD etc). Finally119 patients, 45 patients of Grade-2 COPD [Indacaterol (*n*=23), Tiotropium (*n*=22)] and 74 patients of Grade-3 COPD [Indacaterol (*n*=37), Tiotropium (*n*=37)] were analyzed. The demographics and baseline characteristics in the Indacaterol and Tiotropium group were similar. There was no statistically significant difference between the two groups

in the baseline values of Mean age, Mean FEV_1, Mean symptom score, Mean SGRQ Score (p >0.05) of Grade II and Group III of COPD.

Treatment with indacaterol 150 mcg/day and tiotropium 18 mcg/day improved spirometric variables FEV_1 (Table 1 and 2), *Symptoms Score* (Figure 1 and 2) and *SGRQ Score* (Figure 3 and 4) in both Grade II and III of COPD patients at subsequent follow up to 24 weeks of treatment ($P< 0.001$). However, when inter group comparison (Indacaterol vs. Tiotropium) was made in group Grade-2 and Grade-3 COPD patients, there was statistically no significant difference in FEV_1 *Symptoms Score* and *SGRQ Score* at week of interval till 24 weeks.

Safety assessment

Nasopharyngitis, Upper respiratory tract illness (URTI), tachycardia and tremors were more common in indacaterol group but cough, dry mouth, headache were common in tiotropium group. Fisher's exact test was used to compare ADEs of indacaterol) and tiotropium (p>0.05). The Adverse drug events'distributions in indacaterol and tiotropium group of Grade-2 COPD and Grade-3 COPD patients were 26%, 18% and 24% and 19% respectively. On Naranjo's ADR Probability Scale the events were possible in 19 cases and doubtful in the remaining 7 cases.

DISCUSSION

Once-daily dosing of indacaterol has been approved in some countries for the treatment of patients with COPD.[11] Salmeterol and formoterol having 12-hr duration of action are used twice a day in COPD.[12]

Indacaterol is the first once-daily (150 µg or 300 µg) ultra-long-acting β2-selective agonist used in the treatment of patients with moderate to severe COPD. It has been found to be effective and well tolerated. Tiotropium is also being preferred due to once daily administration than the twice-daily LABA. The studies have shown the efficacy of ultra-long acting indacaterol in patients with moderate to severe COPD and indacaterol improved clinical outcomes to a greater extent than

Table 1: Intragroup and inter group comparison of FEV_1 (L).

(From the baseline and up to 24 weeks follow up in Grade-2 COPD patients)

	Indacaterol *n*=23	Tiotropium *n*=22	Indacaterol vs. Tiotropium *P*-Value
Baseline	1.657±0.424	1.766±0.310	0.2417
2 weeks	1.710±0.420***	1.818±0.299***	0.3279
4 weeks	1.735±0.423***	1.844±0.300***	0.3263
6 weeks	1.753±0.424***	1.860±0.300***	0.3359
8 weeks	1.767±0.426***	1.875±0.300***	0.3330
10 weeks	1.779±0.427***	1.897±0.327***	0.3054
12 weeks	1.791±0.426***	1.909±0.328***	0.3041
14weeks	1.801±0.425***	1.924±0.326***	0.2837
16 weeks	1.811±0.425***	1.934±0.327***	0.2842
18 weeks	1.820±0.425***	1.943±0.326***	0.2837
20 weeks	1.830±0.425***	1.954±0.326***	0.2798
22 weeks	1.840±0.423***	1.966±0.326***	0.2708
24 weeks	1.849±0.420***	1.977±0.327***	0.2618

Values are expressed by mean±SD*** Values are very highly significant (*p*<0.001) when compared with their baseline values.

Table 2: Intragroup and inter group comparison of FEV_1 (L).

(From the baseline and up to 24 weeks follow up in Grade-3 COPD patients)

	Indacaterol *n* = 37	Tiotropium *n* = 37	Indacaterol vs. Tiotropium *p*- value
Baseline	1.024±0.239	1.094±0.244	0.2166
2 weeks	1.076±0.238***	1.148±0.253***	0.2114
4 weeks	1.105±0.235***	1.174±0.257***	0.2321
6 weeks	1.124±0.233***	1.194±0.262***	0.2286
8 weeks	1.140±0.233***	1.209±0.266***	0.2392
10 weeks	1.154±0.233***	1.224±0.271***	0.2383
12 weeks	1.166±0.234***	1.238±0.275***	0.2291
14 weeks	1.179±0.236***	1.251±0.278***	0.2337
16 weeks	1.192±0.236***	1.263±0.280***	0.2421
18 weeks	1.206±0.237***	1.275±0.267***	0.2436
20 weeks	1.227±0.236***	1.289±0.291***	0.3175
22 weeks	1.232±0.235***	1.300±0.292***	0.2735
24 weeks	1.242±0.235***	1.309±0.293***	0.2815

Values are expressed by mean±SD*** Values are very highly significant (*p*<0.001) when compared with their baseline values

tiotropium.[13,14] Donald *et al.* (2015) reported that patients of COPD experience greater benefits with indacaterol than with tiotropium.[15] The results of this study demonstrated that treatment with inhaled indacaterol 150 mcg and tiotropium 18 mcg once daily improved spirometric variable FEV_1 in Grade-2 and Grade-3 COPD. The findings are in consistent with findings of Alam et al. (2015) as they have also observed non-inferiority of indacaterol with tiotropium.[16]

In the intragroup comparison of Grade-2 COPD patients of both the groups, the improvement in mean FEV_1 was statistically significant ($P<0.001$) in subsequent follow up from the baseline values up to 24 weeks of treatment.

Clinical improvement was assessed on the basis of symptom score. There was an improvement in the symptom score in both the groups from the baseline till 24 weeks of treatment and this difference was statistically, highly significant ($p<0.001$) as shown in Table 1 and 2.

Indacaterol decreased the mean symptom score in Grade 2 COPD by 5.6 while tiotropium decreased it by 5.72 after 24 weeks from the pre treatment value, while in Grade-3 patients of COPD, it was decreased by 6.7 and 6.6 from the pretreatment value in indacaterol and tiotropium group respectively. The improvements in indacaterol group as well as in tiotropium group(intragroup comparison) in the symptom score in subsequent follow up at regular 2 weeks of interval till 24 weeks of treatment were statistically highly significant compared to baseline values ($p<0.001$). However, improvements in symptom score between indacaterol and tiotropium (intergroup) was statistically insignificant (Figure 1 and 2). Decrease in mean SGRQ score in the tiotropium as well

as in indacaterol from their respective baseline values to post 24 weeks of treatment was statistically highly significant in the both groups, the Grade-2 and grade-3 COPD patients (Figure 3 and 4).

However, decrease in SGRQ score between the indacaterol and tiotropium group in Grade-2 as well as Grade-3 patients was not statistically significant from baseline values to the 24 weeks of treatment ($p<0.001$). Both treatments were effective and comparable reaching statistical significance in intragroup comparison from baseline to 24 weeks of follow up but there was no significant difference in intergroup (indacaterol vs. tiotropium) at all weeks of follow up. Safety and tolerability were similar across the treatment groups. Although, there were adverse effects seen in both the groups but none of them developed severe and unacceptable adverse effect during the entire study.

Cough following inhalation was fairly common, but did not appear troublesome to patients. Cough immediately following indacaterol and tiotropium inhalation has also been reported previously.[17,18] There was no significant ($p>0.05$) difference between the various adverse events in the both the groups. Tremors were associated with indacaterol group patients (8.1%) while dry mouth with only tiotropium group patients (8%). They were usually mild, often transient and has not caused significant patient withdrawal. Tachycardia was observed with the both treatment groups. It was more in early stage of treatment but in subsequent follow up it resolved. Headache was associated with nasopharyngitis and URTI. These adverse events were consistent with Kolasani *et al.* 2013.[19] In our study indacaterol and tiotropium provided clinically relevant improvements in lung function with comparable safety profiles.
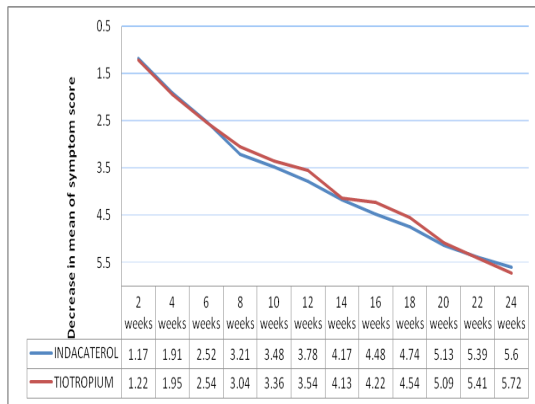

Figure 1: Decrease in the mean value of symptom score.
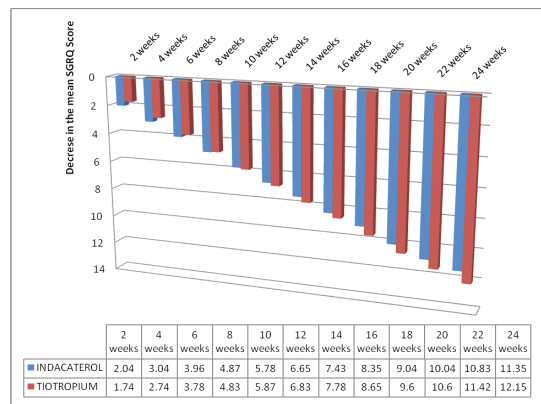(From the baseline up to 24 weeks follow up in grade-2 COPD patients)

	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks	18 weeks	20 weeks	22 weeks	24 weeks
INDACATEROL	1.17	1.91	2.52	3.21	3.48	3.78	4.17	4.48	4.74	5.13	5.39	5.6
TIOTROPIUM	1.22	1.95	2.54	3.04	3.36	3.54	4.13	4.22	4.54	5.09	5.41	5.72

Figure 3: Decrease in the mean value of SGRQ score.
(From the baseline in different follow up in grade-2 COPD patients).

	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks	18 weeks	20 weeks	22 weeks	24 weeks
INDACATEROL	2.04	3.04	3.96	4.87	5.78	6.65	7.43	8.35	9.04	10.04	10.83	11.35
TIOTROPIUM	1.74	2.74	3.78	4.83	5.87	6.83	7.78	8.65	9.6	10.6	11.42	12.15

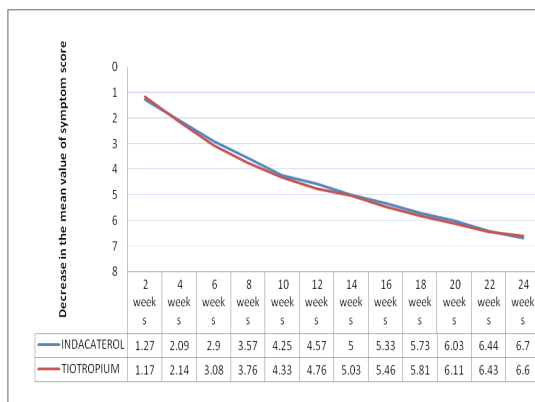**Figure 2:** Decrease in the mean value of symptom score.
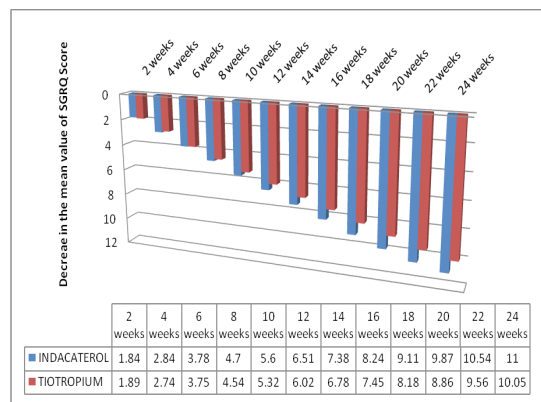(From the baseline up to 24 weeks follow up in grade-3 COPD) patient.

	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks	18 weeks	20 weeks	22 weeks	24 weeks
INDACATEROL	1.27	2.09	2.9	3.57	4.25	4.57	5	5.33	5.73	6.03	6.44	6.7
TIOTROPIUM	1.17	2.14	3.08	3.76	4.33	4.76	5.03	5.46	5.81	6.11	6.43	6.6

Figure 4: Decrease in the mean value of SGRQ score.
(From the baseline in different follow up in grade-3 COPD patients)

	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks	16 weeks	18 weeks	20 weeks	22 weeks	24 weeks
INDACATEROL	1.84	2.84	3.78	4.7	5.6	6.51	7.38	8.24	9.11	9.87	10.54	11
TIOTROPIUM	1.89	2.74	3.75	4.54	5.32	6.02	6.78	7.45	8.18	8.86	9.56	10.05

CONCLUSION

The *indacaterol (*150 mcg once daily) resulted in a *greater improvement* in all tested parameters (FEV$_1$ decrease Symptoms score and decrease SGRQ) *than* inhaled *tiotropium* (18 mcg once daily). However, the difference between *indacaterol and tiotropium groups* was not statistically significant which shows that indacaterol is non-inferior to tiotropium in efficacy and safety profile in Grade-2 and Grade-3 patients of COPD. Further studies, including a larger number of patients, are required in order to confirm findings of present study.

ACKNOWLEDGEMENT

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

COPD: Chronic Obstructive Pulmonary Disease; **DPI:** Dry powder inhalation; **FEV1:** Forced Expiratory Volume in the first second; **FVC:** Forced Vital Capacity; **GOLD:** Global Initiative for Chronic Obstructive Lung Disease; **SGRQ:** St. George's Respiratory Questionnaire; **URTI:** Upper Respiratory Tract Illness.

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