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CICLESONIDE IN ADDITION TO TIOTROPIUM AND FORMOTEROL IN MILD TO MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A RANDOMISED, DOUBLE BLIND STUDY

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is one of the most common lung disease characterised by chronic inflammation of bronchioles. There are very few evidences on use of pharmacotherapy, especially with inhaled corticosteroid, in COPD with FEV_1 > 60%. ***Objective:*** This pilot study was designed to evaluate efficacy and safety of formoterol, tiotropium dual (FT/D) and formoterol, tiotropium, ciclesonide triple (FTC/T) combinations in the cases of COPD with FEV_1 > 50%. ***Methods:*** This was 12 weeks, randomized, double-blind, parallel group study. COPD patients, 35 – 70 years old, with history of smoking ≥ 10 pack years, FEV_1 > 50% of predicted and FEV_1/FVC < 0.7 were included in this study. Eligible patients were randomly allocated to FT/D or FTC/T metered dose inhaler treatment groups in double blind manner. The pulmonary function test, six minute walk test (6 MWT) and adverse event profile were evaluated at every 4 weeks. ***Results:*** Forty-six (23 per group) subjects completed the study and analysed on intent to treat basis. There was significant improvement in FEV_1 and 6 MWD within the group at 12 weeks in both the groups when compared to baseline, while there was not any significant difference between the groups. The FVC was significantly improved in FTC/T treatment group at 12 weeks compared to baseline. There was no significant difference in adverse drug reaction profiles between the groups. ***Conclusion:*** The present study suggests that addition of ciclesonide to formoterol and tiotropium does not improve lung function or exercise endurance more than bronchodilators alone. (CTRI/2011/091/000182).

KEYWORDS: Ciclesonide, Tiotropium bromide, Formoterol, Mild to moderate COPD, Pulmonary function test, Six minute walk test.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide; responsible for 3.2 million deaths annually (44 deaths per 100,000 population).[1] It would become the third leading cause of death globally by 2030 according to World Health Organization (WHO) projection of mortality and causes of death. The rising prevalence of the disease in developed and developing countries of South East Asian region is a concern for World Health Organization (WHO).[1] In India, it is responsible for half a million deaths annually. With increasing use of tobacco smoke, this problem would become worse in future years, especially in developing countries due to scarce resources.[1,2]

As per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, long acting beta agonist (LABA) and anti-cholinergic are the mainstay of treatment for symptomatic improvements in COPD.[3] Anti-inflammatory agents like inhaled corticosteroid (ICS) improves lung function and reduce exacerbation in moderate to severe COPD patients.[4, 5] The combination therapy with ICS and LABA is found to prevent one death for every 36 patients treated.[6] Tiotropium bromide is an anti-cholinergic that is given as once a day administration. It was found to reduce exacerbation and associated hospitalization, improve lung function, health status and pulmonary rehabilitation.[7,8] The combination of LABA with anti-cholinergic may further reduce exacerbation and improve symptoms compared to either drug alone.[9]

The COPD is the chronic disorder which takes years to manifest clinical symptoms and therefore COPD patients often seek treatment late in the course of the disease. COPD is like an iceberg phenomenon. The spirometry evaluation in the community has showed higher prevalence of COPD as compared to clinical observational data.[10] Most of the clinical trials till date

have been performed on moderate to severe cases of COPD.[3] The benefits of the long-term therapy for mild to moderate disease have not been evaluated except for smoking cessation and other non-pharmacological measures.[3] The present study evaluates effects of ciclesonide (ICS) in addition to formoterol (LABA) and tiotropium bromide (anticholinergic) versus formoterol (LABA) and tiotropium bromide (anticholinergic) alone on the spirometry parameters, exercise endurance and safety parameters in mild to moderate cases of COPD.

METHOD

The study protocol was reviewed and approved by Institutional Review Board (IRB), Government Medical College, Bhavnagar (Gujarat), India. The study was carried out at Department of Pulmonary Medicine, Sir Takhtsinhji General Hospital, Bhavnagar between January 2011 and February 2012. Written informed consent was obtained from each participant and all the procedures were conducted in accordance with ICH – GCP guidelines.

Participants

Patients, aged 35 to 70 years of either gender with present or past history of smoking for at least 10 pack-years and confirmed diagnosis of COPD according GOLD guidelines[4] having post bronchodilator forced expiratory volume in 1 second (FEV_1) ≥ 50% of predicted with FEV_1 / forced vital capacity (FVC) < 70% and reversibility < 12% on 400 µg of salbutamol were included in this study.

Patients were excluded, if they met any one of the following criteria: hypersensitive to any of the study medications; use of oral corticosteroid within 6 weeks of the study; history of asthma or any other significant cardiovascular, renal, hepatic or endocrine disorder; pregnant and lactating women; exacerbation during run-in period or contraindication to six minute walk test (6MWT).[11]

Study design

This was a randomised, double-blind, active controlled, parallel group study. After screening (visit 1), eligible patients were enrolled into the study and run-in period (1 week) was started. During screening visit, patients were asked about detailed medical history and were evaluated for eligibility criteria, baseline pulmonary function test (FEV_1, FVC, and FEV_1 / FVC), baseline six minute walk test, vital parameters, detailed general and systemic examination, concomitant medication, routine laboratory investigation (complete blood count, liver function test, renal function test, random blood sugar). After a week of run-in period (visit 2), pulmonary function test and six minute walk test were evaluated. Then subjects were randomly allocated to double blind treatment (1:1) with triple combination (FTC/T, Cipla Ltd. Mumbai, India) metered dose inhaler (MDI) containing formoterol (6 µg/puff), tiotropium bromide (9 µg/puff) and ciclesonide (200 µg/puff) or dual combination (FT/D, Cipla Ltd. Mumbai, India) MDI containing formoterol (6 µg/puff) and tiotropium bromide (9 µg/puff) in dose of one puff once a day for 12 weeks. Drugs were administered at the same time of the day (between 8 a.m. to 9 a.m.) to ensure 24 hr interval between dosing. No other short acting or long acting bronchodilator, anti-cholinergic, oral or inhaled corticosteroids or any combination of these drugs were allowed during run-in or study period.

The randomization list was prepared by a software (Rando 1.2, 2004) for two groups prior to study by a third person. To ensure double-blinding, both identical looking MDI were serially coded and the codes were placed in the opaque serially-labelled sealed envelopes. The participants, research assistant and analyst were blinded to treatment assignment. The codes were opened only at the end of the study or in the case of any serious adverse event.

Outcome measures

Primary endpoint of the study was change from baseline to week 12 in FEV_1. Secondary endpoints include changes in other spirometric parameters (FVC, FEV_1/FVC) and functional status by 6MWT. Patients were followed at every 4 weeks after randomisation,. At each visit, spirometry (FEV_1, FVC, and FEV_1/FVC) and six minute walk test were performed at least 3 hrs after administration of the study drugs. The highest values of FEV_1 and FVC from three technically adequate measurements were retained. Six minute walk test was performed according to American Thoracic Society guidelines.[11] The measurements of vital parameters and general examination were done at each visit. Same laboratory investigations as done on screening visit were performed at the end of the study visit (week 12). All the patients who have appeared for at least 1 visit after starting medication were evaluated for efficacy parameters on the intent to treat (ITT) basis. Missing values were entered by last observation carry forward (LOCF). Safety parameters in the form of any adverse event were noted and reviewed for all the patients who have taken at least one dose of study medications.

Statistical analysis

As clinical and statistical significant improvement in mild to moderate COPD was not known, formal sample size calculation was not done. Data are expressed as mean ± standard error of the mean (SEM), if not specified. All the correlated values were analysed by repeated measures ANOVA or Friedman test with respect to Gaussian distribution of data. Inter-group comparison was done by analysis of co-variance (ANCOVA) with group as factor and baseline data as covariate. Statistical calculations were performed using SPSS 20 (IBM Inc., Chicago, USA; trial version).

RESULTS

Sixty-one patients who entered the run-in period were randomised and 46 completed the study. The flow of the patients during the study has been shown in Figure 1.

The demographic data, baseline lung function data and COPD category are shown in Table 1. All randomised patients were treated and evaluated on the ITT basis provided they have appeared for at least one visit after randomisation. The groups were well balanced at the baseline and there were not any significant difference in demographic, clinical or functional parameters (Table 1).

Table 1: Demographic characteristics of study population

Variable	FT/D (N=23)	FTC/T (N=23)
Age	51.3 (6.25)	52.7 (7.31)
Gender	Male = 23	Male = 23
Post-bronchodilator FEV_1 (L)	1.56 ± 0.47	1.56 ± 0.49
Post-bronchodilator FEV_1 (% of predicted)	74.4 ± 15.3	71.5 ± 15.6
Post-bronchodilator FEV_1/FVC (%)	57.5 ± 9.1	56.6 ± 7.3
Post-bronchodilator FEV_1/FVC (% of predicted)	74.7 ±12.1	73.7± 8.8
COPD severity a) Mild (%) b) Moderate (%)	 8 (34.78) 15 (65.22)	 6 (26.08) 17 (73.92)
Respiratory medication use a) Inhaled anticholinergic b) Inhaled LABA c) Methylxanthines	 5 5 5	 3 3 2

All values expressed as mean ± SD. FEV_1 - Forced expiratory volume in 1 second, FVC - Forced vital capacity, LABA – Long acting $beta_2$ agonist

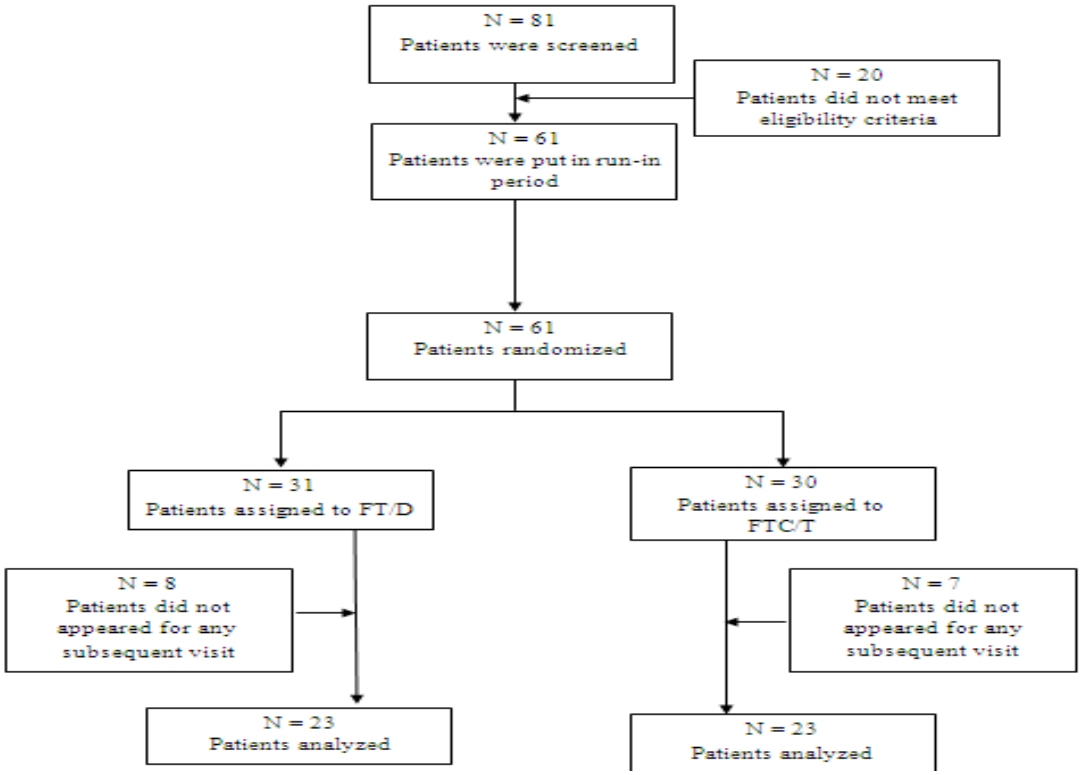

Figure 1: CONSORT diagram

Lung function

The figure 2 shows a curve of increments in FEV_1 from baseline at all subsequent study visits in both the study groups. There was a significant improvement in FEV_1 after 12 weeks of treatment with FT/D (1.73 ± 0.1 vs. 1.56 ± 0.1, $p < 0.01$) as well as in FTC/T (1.75 ± 0.1 vs. 1.58 ± 0.1, $p < 0.05$) when compared with respective baseline values (Figure 2, Table 2). However, there was no significant difference in change from baseline in FEV_1 between the FT/D and FTC/T treated groups at any visit (Table 2). There was no significant improvement in FVC in FT/D treated patients with respect to baseline values. FTC/T treated patients showed significant improvement in FVC (3.1 ± 0.14 vs. 2.8 ± 0.1, $p < 0.05$). FEV_1/FVC ratio was not significantly affected by any drug treatment. However, there was numerically higher

improvement in FT/D treated group as compared to FTC/T treated group. At the screening visit, 65.22% (n=15) and 73.92% (n=17) patients were in the moderate disease category in FT/D and FTC/T groups respectively, which were decreased to 34.78% (n=8) and 39.14% (n= 9) respectively at the end of the study.

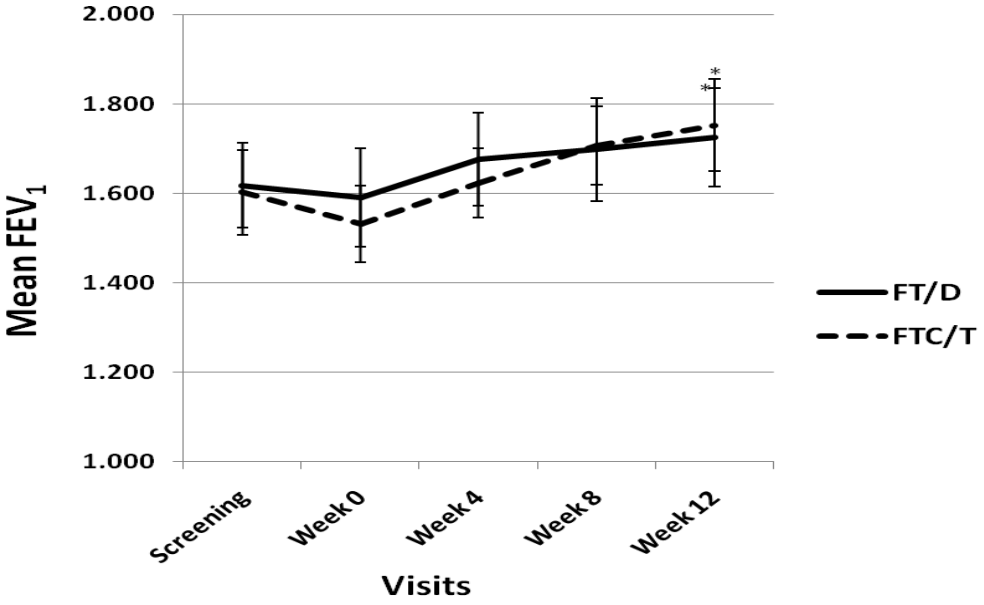

Figure 2: The graph shows FEV1 on screening, week 0, week 4, week 8 and week 12 visits in FT/D and FTC/T groups. There was significant increase in FEV1 at the end of study (Week 12) compared to respective baselines (week 0) in both the groups. (Error bars shows ± 2SEM; *p < 0.05)

Exercise endurance

Six minute walk distance (6MWD) was significantly increased in both the groups. In FT/D treated patients, 6MWD was significantly improved at week 8 (548 ± 15.8, $p < 0.05$) and week 12 (569 ± 13.9, $p < 0.001$) as compared to baseline (509 ± 16.2; Table 2). The FTC/T treated patients also showed significant improvement in 6MWD at week 12 (539 ± 16, $p < 0.001$) as compared to baseline (487 ± 13.4).

Table 2: Treatment effects of the study drugs on spirometry parameters and 6 MWD.

Variable	Week 0	Week 4	Week 8	Week 12
FT/D (n= 23)				
FEV_1 (L)	1.56 ± 0.1	1.68 ± 0.1	1.7 ± 0.1	1.73 ± 0.1**
FEV_1 (% of predicted)	78.3 ± 4.37	82.5 ± 3.94	84.6 ± 4.5	89.6 ± 5*
Mean change from baseline in FEV1	-	0.12 ± 0.03	0.14 ± 0.04	0.17 ± 0.05
FVC (L)	2.7 ± 0.1	2.8 ± 0.2	2.9 ± 0.2	2.9 ± 0.1
FVC (% of predicted)	105 ± 3.9	109 ± 3.8	113 ± 4.3	113 ± 3.5
FEV_1/FVC (%)	56.8 ± 2.1	59.1 ± 2	59 ± 2	59.6 ± 1.9
6 MWD (m)	509 ± 16.2	531 ± 15.6	548 ± 15.8*	569 ± 13.9$^{\#}$
FTC/T (n = 23)				
FEV_1 (L)	1.58 ± 0.1	1.62 ± 0.08	1.71 ± 0.09	1.75 ± 0.1*
FEV_1 (% of predicted)	71.2 ± 2.9	76.6 ± 3.4	82.6 ± 2.9	85.4 ± 3.8
Mean change from baseline in FEV1	-	0.04 ± 0.04	0.13 ± 0.04	0.17 ± 0.05
FVC (L)	2.7 ± 0.1	2.9 ± 0.1	3 ± 0.1	3.11 ± 0.1**
FVC (% of predicted)	99 ± 4.8	106 ± 5.7	111 ± 4.8	116 ± 4.6*
FEV_1/FVC (%)	56.7 ± 1.84	56 ± 1.8	56.7 ± 1.6	56.7 ± 2.1
6 MWD (m)	487 ± 13.4	503 ± 15.9	508 ± 16.6	539 ± 16$^{\#}$

All values expressed as mean ± SEM. *$p < 0.05$, ** $p < 0.01$, $^{\#}p < 0.001$ as compared to baseline by Freidman's test. Inter group comparison was done by analysis of co-variance. FEV_1 _ Forced expiratory volume in 1 second, FVC - Forced vital capacity, 6MWD – Six minute walk distance.

Safety

Incidence of adverse events was similar in both the groups. Three patients from FT/D treated group (n= 31) experienced adverse events. Among these patients, one had exacerbation that was lost to follow up after randomisation visit. This patient had discontinued medication for 15 days before exacerbation. Other two patients had oedema on face and dryness of mouth respectively. Among FTC/T treated subjects (n = 30), one subject withdrew his consent to treatment due to difficulty in using MDI; one subject had tingling and numbness in lower limbs. None of the patient required discontinuation of any of study medications on account of adverse events.

DISCUSSION

This study evaluated effects of ICS, LABA and anti-cholinergic in cases of mild to moderate cases of COPD. At the best of our knowledge, no study reported or recommended use of ICS in cases of COPD with FEV_1 > 60% of predicted.[4,5,12] There is a weak evidence with efficacy of β- agonist and anti-cholinergic in cases of COPD with FEV_1 > 60% of predicted.[9,13] This is the first pilot study of its kind to explore the effects of LABA, anti-cholinergic and ICS in cases of COPD with FEV_1 > 60% of predicted (78.39 ± 4.37 in FT/D and 71.17 ± 2.91 in FTC/D groups).

The FT/D and FTC/T combinations improved FEV_1 in mild to moderate cases of COPD in present study. These results are consistent with previous studies reporting improvement in FEV_1 in moderate to severe cases of COPD as compared to placebo.[8,14] In present study, FTC/T could not show any significant improvement in FEV_1 over FT/D. ICS were found to improve lung function, quality of life and rate of exacerbation in long-term studies.[14] The rationale behind using corticosteroids in COPD is to reduce inflammation and thereby support bronchodilators. In addition, the corticosteroid increases sensitivity to β-agonist activity.[15] However, many of previous clinical trial showed minimal or no corticosteroid effect on lung function. The possible explanation for these conflicting observations may be impairment of corticosteroid receptor by continual oxidative stress caused by smoking as well as chronic inflammatory state.[16] This may result in reduced or delayed corticosteroid response and explain why we could not detect any improvement in lung function in term of FEV_1 in FTC/T treated patients compared to FT/D treated patients, with relatively short duration of treatment.

Interestingly, FTC/T improved FVC when compared to baseline values. The clinical significance of FVC is not much elaborated in obstructive lung diseases. The severe cases of COPD have usually associated restrictive component and reduced FVC. Thus, this observation is important in cases of severe COPD or COPD with restrictive component. The long-term importance of FVC in mild to moderate cases of COPD is yet to be elucidated.

Both the FT/D and FTC/T treatments improved exercise endurance in term of 6MWD however there was no significant difference between the treatments. 6MWD is a surrogate marker for quality of life and functional capacity.[17] It declines rapidly in the later course of COPD with severe airflow limitation. Even FEV_1 decline is less pronounced as compared to functional loss in terms of 6MWD.[18] Thus, 6MWD is a better predictor than FEV_1 in COPD in term of functional capacity.

Prescribing ICS in addition to long acting bronchodilators to COPD patients with $FEV_1 \geq 50\%$ (GOLD stage I and II) of predicted is common practice to reduce exacerbation.(19, 20) However, the findings of a meta-analysis suggest that these patients do not require additional therapy to reduce exacerbation.[21] The present study further adds to existing evidence that addition of ICS does not cause significant improvement in lung function, in terms of FEV_1 and 6MWD in similar patients. The information on balance between benefits and risk of the corticosteroid is complex and not straightforward in these patients. However, recent studies have reported increased risk pneumonia in COPD patients taking ICS.[22,23] Therefore, decision for choosing treatment for mild to moderate COPD patients should be limited to bronchodilators. Placebo could be excluded as offering no treatment is not in best interest of the patients.[21] Currently, GOLD guidelines recommend using short acting bronchodilators (as and when necessary) as first line therapy and LABA or LAMA as an alternative therapy.[3] Present study showed functional improvement with combination of long acting bronchodilators in patients of mild to moderate COPD, therefore it is advisable to offer LABA or LAMA to patients with even mild COPD to improve exercise tolerance. Evidence suggests that improvement in exercise tolerance is associated with improvement in quality of life. This can be correlated with conversion of moderate to mild COPD with treatment in the current study. In general, the cost of therapy with additional ICS to bronchodilators therapy is more compared to bronchodilator alone. This further favours use of bronchodilators alone in mild to moderate COPD patients, in absence of strong evidence on benefits of ICS in these patients.

The present study showed no significant difference concerning incidence of adverse events between the groups. This may be due to the fact that the study was not powered enough to detect subtle differences in adverse events incidences.

This study has several limitations due to its small sample size and relatively short duration of treatment. However, it is the first of its kind study that showing functional (exercise) improvement with combination of bronchodilators in relatively less severe COPD. Based on

this, it is prudent to evaluate whether early institution of long acting bronchodilators in mild to moderate COPD can slow down the progression of GOLD I patients towards GOLD IV. A study with longer duration of treatment and larger sample size is required to further explore the effects of different combinations of LABA, LAMA and ICS in mild to moderate COPD. Additionally, large clinical trials are can also delineate risk-benefits profile of LABA and LAMA alone in mild COPD and its combination in mild to moderate COPD.

In conclusion, both the FT/D and FTC/T improve lung function and exercise endurance in mild to moderate patients of COPD as compared to baseline values. However, there is no significant benefit of adding ICS to inhaled bronchodilators in these patients.

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