



A preliminary randomized open labeled comparative analysis of efficacy & safety of inhaled Tiotropium and Tiotropium plus Formoterol in COPD

Muzaffer Ahmad Pukhta, Zubair Ahmad Ashai, Mushtaq Ahmad Shah, Zaffar Abbas, Samina Farhat, Shakeel Ahmad Mir, Z. Singh, Vishal R. Tandon

Abstract

A randomized, open labeled comparative analysis for 2-week therapy of inhaled Tiotropium (T) (n=30) and Tiotropium plus Formoterol (TF) (n=30) once daily was carried in stable COPD patients. Objective parameters like lung functions (FEV1 and FVC), SBP, DBP, pulse and subjective parameters like improvement in respiratory symptoms & safety were assessed at baseline and after 2 weeks of treatment. Mean FEV1 was 1.0963 ± 0.3826 & 1.1657 ± 0.3701 as well as 1.1227 ± 0.4129 & 1.2260 ± 0.3830 before & after treatment with inhaled T & TF respectively. A statistically significant $p < 0.05$ and $p < 0.001$ improvement was only observed for FEV1 without significantly affecting other study parameters with two treatment modalities respectively when analyzed from respective base lines. However, on comparing the post drug improvement in objective & subjective parameters among T & TF treatment arms showed statistically insignificant $p > 0.05$ variation. Both the regimens were well tolerated and no case warranted withdrawal of treatment. The present study suggests that in the treatment of COPD, inhaled long acting bronchodilators (T & TF) on comparison appear equally effective & safe.

Key Words

COPD, Tiotropium, Formoterol, Bronchodilators, Lung Function

Introduction

COPD is a most common disease affecting many people worldwide. It is a 4th leading cause of death worldwide. Globally by 2020 it is projected to rise to 3rd position as a cause of death. Worldwide Prevalence of COPD ranges from 4-6%(1). India Prevalence is documented up to 4.1 % with Male(5%) & Female (3.2%)(2). Study from Kashmir pointed to a higher prevalence of 7.55% in smokers and 10.56% in people living in poorly ventilated houses (3). Overall COPD imposes a great socioeconomic burden. Among the various bronchodilators available, the long acting bronchodilators are the first choice option for the treatment of stable COPD (4). Presently, two types of inhaled long-acting bronchodilators are available for clinical use: the long-acting beta-2 agonists (LABAs) Formoterol and Salmeterol and the new long-acting anticholinergic Tiotropium(5). It has been demonstrated that the combination of the short-acting beta-2 agonist Salbutamol with the short-acting anticholinergic Ipratropium is

superior to either single agent alone (6) as such one can expect that combination therapy with the long-acting drugs may achieve even greater benefit. Limited clinical data on combination therapy of Tiotropium and an inhaled long acting beta-2 agonist Formoterol in COPD has prompted us to study the effect of add on therapy of Formoterol on efficacy and tolerability in patients with stable COPD on Tiotropium.

Materials and Methods

The study was conducted at chest diseases hospital Srinagar and was a randomized, open labeled study design with 2-week treatment periods (Fig 1). Approval from the hospital medical ethics committee and written informed consent from patients were obtained before medication washout or any study procedure. Patients having a clinical diagnosis of COPD according to the American Thoracic Society (ATS) criteria were selected (7). The patients had to show a stable airways obstruction with $FEV1 < 60\%$ of predicted, and an FEV1/FVC ratio

From the Department of Pharmacology, Govt Medical College, Srinagar, (J&K)-India

Correspondence to : Dr.Muzaffer Ahmad Pukhta Senior Demonstrator, Department of Pharmacology, GMC, Srinagar, J&K-India.

< 70% (8). The patients had to be at least 40 years old, and all had to be current or previous smokers (>10 pack-years). The exclusion criteria of the study shown in Fig 1 from the study.

After initial screening (visit 1), patients returned for a second clinic visit (visit 2) and base line investigations and FVC and FEV1 were measured. Long-acting inhaled beta-2 agonists were not allowed for at least 48 h, and short-acting anticholinergics or beta-2 agonists for at least 8 h before the second visit and the spirometric baseline measurements. While performing the FVC maneuver a cough, an inspiration, a Valsalva maneuver, a leak, or an obstructed mouth piece disqualified the trial and the test was repeated. The patients entered a 2-week pretreatment period of T, 18 µg qd inhalation powder in order to achieve a pharmacodynamic steady state of T (9) Subsequently, treatment with T 18 µg qd in the morning to one group (R1) and Tiotropium 18 µg qd plus Formoterol 12 µg once daily dry powder inhalation capsule in the morning to the second group (R2) were given. The patients returned for clinical examination at an interval of one week during the study period. During this visit they were asked about the change in symptoms and about any adverse drug effects. Adverse events were recorded and monitored throughout the study. An adverse event was defined as any symptom, physical sign, syndrome, or disease that occurred after start of treatment with the study drug or was present at the start of treatment with the study drug and worsened. Patients underwent a physical examination at the screening visit and at each subsequent visit. Blood pressure and heart rate were also recorded (10). At the end of 2 weeks the post-drug spirometry was performed after the study medication was inhaled in the presence and under the supervision of the trial physician, keeping the pulmonary technician blinded for the inhaled medication. Furthermore, the patients did not communicate to the pulmonary technician which study medication was inhaled. The Spirometer used during the study was PC based RM Medispiror, manufactured by Recorders & Medicare Systems Chandigarh. The spirometer fulfilled ATS criteria for accuracy and precision. The Spirometry testing was performed according to the guidelines prescribed in the America Thoracic Society (ATS) guidelines (11). For conducting the Spirometry the open circuit method was used.

Measurement

The objective evaluation of the effectiveness was done by evaluating the improvement in the various spirometric values like FVC and FEV1(12). Subjective evaluation of effectiveness was done by asking the patient about the

change in symptoms of cough and breathlessness. The patients were graded into the following three categories according to the change in symptomatology i.e. Improved (I) No Change(NC) and Worse(W) (13,14). The objective assessment of the tolerability was done by noting the change in pulse and B.P. Subjective assessment of the tolerability was done by noting various side effects (15).

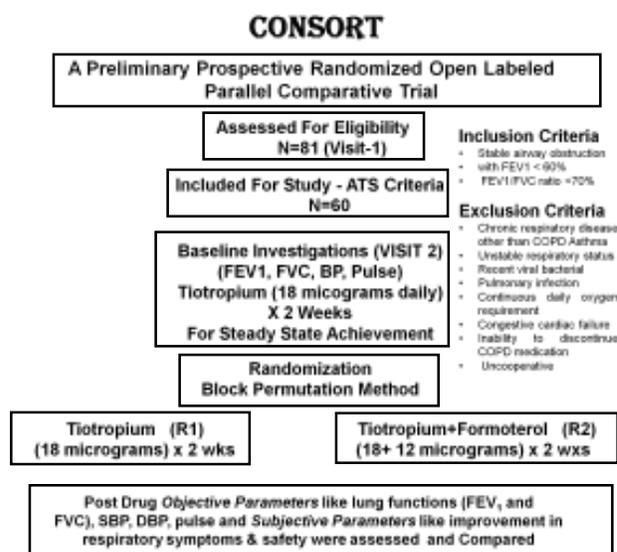
Statistical Evaluation

Statistical evaluations were accomplished with paired t tests for before and after treatment results of R1 and R2, while ANNOVA was used for comparing after treatment results of R1 and R2. Chi square test was used for evaluating the subjective improvement as well as adverse effects reported by patients of R1 and R2. Continuous data is reported as mean±standard deviation. A p value of <0.05 was considered significant and a p value of <0.001 was considered highly significant. Data from patients withdrawn early were included in the analyses up to the time of study discontinuation. No interpolation was used for the missed data. The primary efficacy endpoint was FEV1 response at the end of the 2-week treatment period. FEV1 response was defined as the change from baseline at the end of the 2 week treatment. Baseline FEV1 was the pre-treatment FEV1 measured at Visit 2, 10 minutes prior to administration of the first dose of the study medication.

Results

A total of 81 patients were screened; 60 of them were eligible according to ATS criteria and entered the study. Of the 60 randomized patients, 58 completed the study and 2 discontinued prematurely as they did not report for

Fig.1.



post drug spirometry. The demographic profile and base line characteristics of the study population are shown in *table 1*.

Objective parameters like lung functions (FEV1 and FVC), SBP, DBP, pulse and subjective parameters like improvement in respiratory symptoms & safety were assessed at baseline and after 2 weeks of treatment. Mean FEV1 was 1.0963±0.3826 & 1.1657±0.3701 as well as 1.1227±0.4129 & 1.2260±0.3830 before & after treatment with inhaled T & TF respectively. A statistically significant $p < 0.05$ and $p < 0.001$ improvement was only observed for FEV1 without significantly affecting other study parameters with two treatment modalities respectively when analyzed from respective base lines. However, on comparing the post drug improvement in objective & subjective parameters among T & TF treatment arms showed statistically insignificant $p > 0.05$ variation. Both the regimens were, however, well tolerated as no case warranted withdrawal of treatment.

The effect of two regimens on various study parameters are shown in *table 2* & *3* and *Fig 2*.

Discussion

The long-acting bronchodilators are more effective and convenient than short-acting bronchodilators. It is also emphasized that combining bronchodilators may improve efficacy without increasing the risk of side effects compared to increasing the dose of a single bronchodilator (16). Inhaled anticholinergic drugs are often recommended for use as a first-line therapy for patients with COPD because they provide similar or more effective bronchodilating actions, as well as fewer side effects as compared to other bronchodilators (17). The use of T is a safe and effective once-daily anticholinergic bronchodilator and is useful as first-line therapy in COPD (18). A significant body of evidence supports the use of long-acting beta-2 agonists and anticholinergic agents in reducing exacerbations in patients with moderate to severe COPD (19).

The present study investigated the additional effects of Formoterol once daily inhaled in patients receiving T. Our results showed a statistically significant improvement in FEV1 with both the regimens but the improvement with regimen R2 was highly significant ($p < .001$). These results correlate well with other studies which also found a significant improvement in FEV1 and FVC with T and TF. The improvement in FEV1 was higher on addition of Formoterol to Tiotropium (16). Same results were shown by other studies (20,21). Various studies have shown that in patients with COPD a significant improvement in FEV1 occurs after treatment with T (16,22,23). Bronchodilators may increase FEV1, FVC or exercise tolerance, but an increase in FEV1 does not correlate

Table 1. Demographic Characteristics of Study Population

Variable (n=60)	Data
Male/Female (%)	81/19
Age (Mean±SD)	61±6
Smoking History, pack-yr (Mean ±SD)	24 ±6
Duration of Disease (years) (Mean ±SD)	12 ±4

Table 2. Comparative Effects of R1 & R2 on Objective Parameters

Groups	Before Treatment (Mean±SD) L	After Treatment (Mean±SD) L	t	p
FEV1				
R1	1.0963±0.382	1.165±0.3701	2.284	<0.05
R2	1.1227±0.412	1.226±0.3830	5.351	<0.001
ANOVA df 1,58 F=0.643 p>0.05				
FVC				
R1	2.1813±1.071	2.587±1.1873	2.102	<0.05
R2	1.9653±0.800	2.2350±0.757	2.184	<0.05
ANOVA df 1,58 F=0.965 p>0.05				
Pulse				
R1	70.466±1.074	70.166±2.889	0.670	>0.05
R2	70.166±2.889	70.400±1037	0.492	>0.05
ANOVA df 1,58 F=0.025 p>0.05				
Systolic BP				
R1	122.13±8.850	122.500±7.39	0.346	>0.05
R2	122.40±7.398	121.800±8.32	0.742	>0.05
ANOVA df 1,58 F=0.114 p>0.05				
Diastolic BP				
R1	78.066±5.445	78.266±4.883	0.532	>0.05
R2	78.400±4.965	78.0866±5.44	0.841	>0.05
ANOVA df 1,58 F=0.003 p>0.05				

Fig 2. Comparative Effects of R1 & R2 on Subjective Symptoms

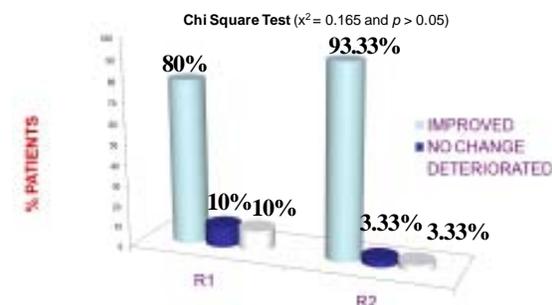


Table 3. Adverse Effects of R1 & R2

Side Effects n(%)	R1	R2
Dry mouth	8(26.66)	7(23.33)
Headache	3(10)	3(10)
Dizziness	1(3.33)	(0)
Tremor	(0)	2(6.66)
Palpitations	(0)	1(3.33)
Total	12(40)	13(43.33)

well with an improvement in symptoms (24). In our study the improvement in FEV1 and percentage improvement (*Fig-2*) in respiratory symptoms correlated well in both the regimens. However, the improvement in symptomatology was statistically insignificant ($\chi^2=0.165$,



$p > 0.05$). The objective tolerability of the two regimens in the present study revealed that both regimens caused statistically insignificant changes in vital signs viz. pulse rate, systolic blood pressure and diastolic blood pressure. (Table 2) These findings corroborated well with the finding of other studies on TF (16,10). Regarding the safety, various other studies also showed almost same percentage of side effects with these drugs (13,15,25) as shown by current study. The results of the present study need to be substantiated with long-term studies to establish whether the improvements in lung function translate into improvements in clinical outcomes such as symptom scores, health status, exercise tolerance, exacerbation rates and the long term safety profile which have been the limitations of the present study.

Conclusion

The present study suggests that in the treatment of COPD, inhaled long acting bronchodilators (T & TF) on comparison appear equally effective & safe. Thereby, suggesting no advantage of adding Formoterol to Tiotropium

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