Original Article

Comparison of efficacy between long-acting beta 2-agonists (formoterol fumarate) and leukotriene-receptor antagonists (montelukast) as add-on therapy to inhaled corticosteroids (budesonide) in moderate persistent asthma

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ABSTRACT

Objective: This study was aimed to compare the efficacy between long-acting beta 2-agonists and leukotriene receptor antagonists as add-on therapy to inhaled corticosteroids in moderate persistent asthma. **Materials and Methods:** This study was carried out at the Kovai Medical Center and Hospital, in Coimbatore. The study protocol was approved by the Ethics committee of the Kovai Medical Center and Hospital. Patients with asthma in the outpatient respiratory department were included in the study. Out of 100 patients, 46 patients received the combination product, budesonide 400 μg and formoteral fumarate 6μg as an inhaled dose and this group was named group A. The other group had 44 patients and was prescribed oral montelukast 10 mg along with budesonide 400 μg as an inhaled dose. This group was called group B. The parameters recorded included, pulmonary function test reports, MBDS (Modified Borg's Dyspnea Scale). The quality of life was evaluated both before and after the treatment period by the SGRQ (St. George's Respiratory Questionnaire). **Results:** The two groups, group A and group B were assessed for pulmonary activity. The initial results of the score (MBDS) were 3.3 ± 0.12 and 3.2 ± 0.13 for group A and group B, respectively. Scores were reduced to 0.19 ± 0.08 and 0.35 ± 0.08 respectively after one month of therapy. For group A, the mean values for forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF) and forced vital capacity (FVC) before treatment were 1.4 ± 0.1, 3.2 ± 0.33 and 1.8 ± 0.18, respectively, whereas after treatment the values were 2 ± 0.14, 5.2 ± 0.41 and 2.4 ± 0.17. For group B the mean FEV_1, PEV and FVC, before and after therapy were 1.2 ± 0.1 - 1.8 ± 0.17; 3.1 ± 0.3 - 5.4 ± 0.42; 1.8 ± 0.17 - 2.4 ± 0.22 respectively. **Conclusions:** In our conclusion, we suggest that a montelukast is as effective as formoterol fumarate for add-on therapy to budesonide in moderate persistent asthma. Hence, montelukast can be considered an alternate therapeutic option for such patients. The results of this study are expected to provide physicians with clinical evidence to help them make a rational decision when treating patients with moderate persistent asthma.

Key words: Budesonide, formoterol fumarate, moderate persistent asthma, montelukast

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INTRODUCTION

Corticosteroids were introduced for the treatment of asthma shortly after their discovery in the 1950s and remain the most effective therapy available for asthma. The initial choice of anti-inflammatory therapy in

asthma is an inhaled corticosteroids (ICSs).[1] The prescribed initial dose often reflects the physician's clinical assessment of asthma severity. Once the initial dose of ICS has been determined, clinicians must choose an appropriate strategy, if the patient continues to be symptomatic.[2] In the first British guidelines on asthma management, high dose of ICS was the only option at step3. Recent review of these guidelines suggests addition of inhaled LABA (long-acting beta 2 agonists) that were added as an alternative to increase in dose of ICS.[3] Long-term studies support this approach in which leukotriene receptor antagonist and theophylline are also the potential contenders. Inhaled LABA, by definition, have duration of action of at least 12 hours in contrast to short acting beta2 agonists, which act for 4-6 hours.[4] They cause smooth muscle relaxation, decrease mucosal permeability, enhance mucociliary clearance and decrease the release of inflammatory mediators from mast cells and eosinophils. Inhaled LABA should be considered when standard introductory doses of ICS fail to achieve control of asthma before raising the dose of ICS.[5] However, long-term treatment with inhaled LABA does not appear to influence the persistent inflammatory changes in asthma, and hence this therapy should always be combined with ICS, and addition of inhaled LABA to a daily regimen of ICS improves lung function and effective asthma control than increased dose of ICS. LTRA (Leukotriene receptor antagonists) are a new class of anti-inflammatory drugs, which interfere with leukotriene production or leukotriene receptor.[6] The pathology of asthma is associated with the recruitment and influx of inflammatory cells such as eosinophils into airways and lung tissues.[7] Activated eosinophils release pro-inflammatory mediators such as cytokines and cysteinyl leukotrienes. Treatment with anti-leukotrienes has been shown to result in significant reduction in the concentration of eosinophils in the sputum and peripheral blood of asthma patients, implying a role for eosinophils in inflammatory processes associated with asthma.[8] LTRA, have been demonstrated to possess bronchodilating and anti-inflammatory properties this makes these drugs ideal candidates for the treatment of asthma. The last 1998-updating of the GINA (Global Initiative for Asthma) guidelines for the diagnosis and therapy of asthma recommends the use of LTRAs in the treatment of moderate and mild asthma. In patients with moderate asthma not completely controlled with moderate doses of ICS, the addition of an LTRA is indicated as an alternative to either the increase of the ICS dose or the addition of an inhaled LABA.[9] This study was aimed to compare the efficacy between LABA and LTRA as add- on therapy to ICS in moderate persistent asthma.

MATERIALS AND METHODS

This study was a parallel group open label study, carried out at the Kovai Medical Center and Hospital, in Coimbatore. The study protocol was approved by the Ethics committee of the Kovai Medical Center and Hospital. Patients with asthma in the outpatient respiratory department were included in the study. Patients gave their consent prior to inclusion in the study. Patients aged 18 to 70 years of age having a history of chronic asthma were eligible. They were further screened and only those patients with step3 asthma symptoms as per the GINA guidelines were selected. Other inclusion criteria included forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio (FEV_1/FVC) of less than 75% of predicted, FEV_1 of 40-60% of predicted and an improvement of 12% or more in FEV_1 after using a β-agonist (salbutamol, 400 μg).[10] Patients were excluded if they had significant co-morbidities, were receiving oral corticosteroids, LABAs, leukotriene antagonists or theophylline or had undergone an asthma exacerbation or lower respiratory tract infection within the four weeks prior to study entry. Children and pregnant women were also excluded.[11] A placebo was not included, because the study was designed as a comparison and it would be ethically inappropriate not to provide active treatment to patients with such chronic systems.[12] A total of 831 asthma patients visited the outpatient respiratory department of the hospital during this study period. Of these patients, 371 were diagnosed with mild intermittent asthma, 180 patients were diagnosed with mild persistent asthma, 158 patients were diagnosed with moderate persistent asthma and 122 patients were diagnosed with severe persistent asthma. According to the inclusion criteria, 104 patients with moderate persistent asthma were identified and enrolled in the study. From these 104, 4 patients were excluded for exacerbation of asthma symptoms along with viral fever. Out of 100 patients, 46 patients received the combination product, budesonide 400 μg and formoteral fumarate 6 μg as an inhaled dose and this group was named group A. The other group had 44 patients and was prescribed oral montelukast 10 mg along with budesonide 400 μg as an inhaled dose. This group was called group B. Patients were divided into two groups. One group received a combination product, budesonide (400 μg) and formoterol fumarate (6 μg) as a single inhaled dose,

while the other group received budesonide (400 µg) inhaled dose and montelukast (10 mg) as an oral dose. Patients' demographics, history of disease, medical history, social habits, and lung function test reports were documented.[13] Patients were counseled about asthma and trained on how to use an inhaler, in order to optimize therapy. Monitoring of patient status in each group was done after one month. The parameters recorded included, pulmonary function test reports, MBDS (Modified Borg's Dyspnea Scale).[14] The quality of life was evaluated both before and after the treatment period by the SGRQ (St. George's Respiratory Questionnaire).[15] Symptoms were measured by the daily diary card and compliance assessed by the countable method. The primary end-point of the study was spirometric measures of pulmonary function after one month from the screening period. Daily diary card was provided to the patients that helped in assessing the quality of life.

Statistical analysis

Comparison of the drug effects before and after treatment, in context to their improvement of lung function parameters, was done by paired '*t*' test.[16] The effect of these two regimens on quality of life was assessed by the paired '*t*' test. The effectiveness of the therapies was done by Chi-square test.[17] Independent variables were expressed as percentages. Statistical significance was set at $P < 0.05$.[18]

RESULTS

The baseline characteristics, of both groups were the same except that the numbers of female patients were higher in group B than group A. This difference was reflected in higher absolute values for pulmonary function in the group B at baseline. Demographic characteristic of the patients is given in Table 1.

Study revealed that the number of patients visiting the hospital was more in the onset of winter than in summer. The two groups, group A and group B were assessed for pulmonary activity. The results of the MBDS have been shown in Table 2. The mean values of FEV1, PEF (Peak expiratory flow) and FVC before treatment for group A and B have been shown in Table 3.

Both treatment groups were found to improve lung function and dyspnea index significantly ($P < 0.05$). The improvement in group B was found to be equally good as that in group A. The assessment of quality of life (SGRQ score) for groups A and B before and after treatment have been shown in Table 4. Quality of life was assessed by symptoms score, activity score, impact score and the total score. In both group A and B, there has been a significant ($P < 0.05$) decrease in the individual scores. The mean total score for group A before initiation of treatment was 52.52 ± 2.7, which was reduced to 7.33 ± 1.7 after one month of therapy. For group B there was also a significant ($P < 0.05$) reduction in total score from 60.65 ± 3 to 12.06 ± 2.3. Results show a significant ($P < 0.05$) improvement in the quality of life in both treatment groups. However, group A had a better efficacy than group B and it has been shown in Table 4.

Table 1: Demographic characteristic of the patients

Demographic data	Percentage	
	Group A	Group B
Gender		
Female	71	50
Male	29	50
Occupation		
Agriculture	7	25
House wife	50	25
Polluting occupations	14	33
Others	29	17
Family history of asthma		
With family history of asthma	43	42
Without family history of asthma	57	58
Co-morbidities		
Co-morbidities	79	67
Others	21	33
Social habits		
Smoker	29	8
Nonsmoker	71	84
Obesity		
Normal	50	67
Over weight	29	33
Obese	21	00
Asthma duration (years)		
<10	50	58
≥10	50	42

Table 2: Values of the modified borg's dyspnea scale scores obtained on the first and second visits with Group A and Group B *$P<0.05$

Visit	First visit		Second visit	
	Group A	Group B	Group A	Group B
MBDS score	3.3	3.2	0.19	0.35

MBDS=Modified borg's dyspnea scale

DISCUSSION

According to current asthma guidelines, two different treatment options are available if asthmatic patients remain symptomatic. One is by adding another drug (e.g., LABAs or a leukotriene receptor antagonist,

Table 3: Forced Expiratory Volume1, Peak Expiratory Flow, Forced Vital Capacity values obtained on the first and second visits with group A and group B

Visit	FEV_1		PEF (liter)		FVC (liter)	
	Group A	Group B	Group A	Group B	Group A	Group B
First	1.4±0.1	1.2±0.1	3.2±0.33	3.1±0.3	1.8±0.18	1.8±0.17
Second	2±0.14*	1.8±0.17*	5.2±0.41*	5.4±0.42*	2.4±0.17*	2.4±0.22*

Values are expressed as mean±S.E *P<0.05, FEV=Forced expiratory volume, PEF=Peak expiratory flow, FVC=Forced vital capacity

Table 4: Changes from the baseline in the symptoms, activity, impact and total scores of the patients on group A and group B therapies

SGRQ score	Group A		Group B	
	Before	After	Before	After
Symptoms	64.02±3.6	5.42±2.1*	74.08±3.9	13.34±3.3*
Activity	53±2.5	8.23±3.3*	60.03±3.2	13.35±3.6*
Impact	48.35±3.6	6.85±1.6*	56.41±3.6	10.91±1.5*
Total	52.52±2.7	7.33±1.7*	60.65±3	12.06±2.3*

Values are expressed as mean±S.E *P<0.05, SGRQ=St. George's Respiratory Questionnaire

or theophylline) to the treatment regimen. The second alternative is increasing the dose of the ICS (Wettengel *et al*., 2008). Patients with step3, moderate persistent asthma who are symptomatic while receiving ICS therapy, require additional medication. Our study is an open label parallel group prospective study designed to compare the effectiveness of two different add-on therapies - budesonide 400 µg/formoterol 6 µg in a single inhaler (group A) and budesonide 400 µg (inhaled)/montelukast 10 mg (oral) (group B) in moderate persistent asthma. In our study, we found that addition of montelukast, a leukotriene receptor antagonist, to the treatment of patients who continue to experience symptoms while on an ICS, was found to be equally effective as adding formoterol, a LABA to an ICS.

Studies have shown that addition of montelukast could lead to a reduction in ICS dose without a significant decrease in peak expiratory flow rate, while maintaining asthma control over a 24-week period. Therefore, montelukast may be useful for long-term treatment in patients with asthma who require high doses of inhaled corticostroids (Tohda *et al*., 2002). In patients with mild airway obstruction and persistent asthma symptoms, despite treatment with budesonide in doses of 400-1600 µg by Turbuhaler, concomitant treatment with montelukast provides significant additional benefit (Vaquerizo *et al*., 2003). One group of workers has demonstrated that although montelukast gives effective protection, it is not superior to that of the LABAs (Fish *et al*., 2001). Others have found that addition of montelukast to patients whose symptoms remain uncontrolled with inhaled fluticasone could be as effective as adding salmeterol in protecting against asthma exacerbations (Bjermer *et al*., 2006). Our results are consistent with those of Bjermer *et al*. Lung function improved in both treatment groups. Researchers are divided on which group improves lung function more. Some groups have noticed the LABAs to have better action in this regard (Fish *et al*., 2001; Condemi *et al*., 1999) while others have reported that the add-on leukotrientes have a more or less similar improvement (Bjermer *et al*., 2003; Lipworth and Jackson, 2002) In our studies the parameters studied FEV1, PEF and FVC significantly improved with both additions and the improvement did not differ significantly between the groups.

Quality of life is an important measure in asthma therapy as it gives an idea about how medication helps the person to lead an undisturbed normal life with the disease. In our study, both montelukast and formoterol, improved the quality of life of the patients as is evident from the scores obtained. However, improvement is significantly better with group A than B, which is also observed by other workers (Nelson *et al*., 2001; Busse *et al*., 1999).

CONCLUSIONS

In our conclusions, we suggest that a montelukast is as effective as formotorol fumerate for add-on therapy to budesonide in moderate persistent asthma. Hence, montelukast can be considered to be an alternate therapeutic option for such patients. The results of this study are expected to provide physicians with clinical evidence to help them make a rational decision when treating moderate persistent asthma patients. Based on this, the best approach for the clinician is to individualize treatment for each patient by considering clinical needs, comorbidities and lifestyles.

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