RESEARCH ARTICLE

COMPARATIVE EVALUATION OF MODERATE DOSE INHALATIONAL CORTICOSTEROID (ICS) FLUTICASONE WITH THE COMBINATION OF LOW DOSE FLUTICASONE AND MONTELUKAST IN MODERATE PERSISTENT BRONCHIAL ASTHMA

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ABSTRACT

Background: Use of inhaled corticosteroids (ICS) are recommended in all grades of persistent asthma and once the symptoms are stabilized, "stepping down" of steroids is recommended to minimize their unwanted effects with the addition of a second medication with a complimentary mechanism of action.

Aims & Objective: In our study a comparison of moderate dose ICS Fluticasone in "stepping down" strategy with combination of low dose Fluticasone with once-daily montelukast were assessed.

Materials and Methods: 50 patients with moderate persistent asthma were randomly assigned in study. Initially stabilized on fluticasone propionate (FP) 250 µg twice daily, for four weeks, there after patients were given the medication as per the protocol Group-I (n=25)- fluticasone 250µg BD; Group-II (n=25)- fluticasone125 µg BD + Montelukast 10 mg in night. Patients were then followed up for 12 weeks. The primary efficacy variables were changes in FEV1%, PEFR%, ACS (asthma control symptom) score and asthma quality of life (QOL) score.

Results: Changes in lung function at the end of study in Group-I and Group-II respectively as compared to 0 week (baseline) values, FEV1% value ($p < 0.05$, $p < 0.05$), PEFR% value ($p < 0.01$, $p < 0.05$), ACS score ($p < 0.01$, $p < 0.05$), AQOL score ($p < 0.05$, $p < 0.05$). ICS fluticasone 250 µg BD and low dose fluticasone 125 µg BD + Montelukast 10 mg in night are equally efficacious in improving lung functions, asthma symptoms and QOL. Montelukast group was more expensive with fewer adverse events.

Conclusion: Moderate dose fluticasone did not show any benefit over combination of low dose fluticasone and Montelukast 10mg in night. Montelukast 10 mg in combination with low dose fluticasone can be an alternative in moderate persistent asthma.

Key Words: Bronchial Asthma; Inhalational Corticosteroids; Stepping Down Strategy; Montelukast

Introduction

Airway inflammation is considered to be an integral part of the pathogenesis in patients with all grade of persistent bronchial asthma.[1] Corticosteroids are the most effective anti-inflammatory agents currently available for the treatment of asthma.[2] Several clinical studies have demonstrated that inhaled corticosteroid (ICS) therapy improves lung function, reduces airway hyper-reactivity[3], and mediates a marked reduction in inflammatory mediators in the bronchial epithelium and sub-mucosa[4]. Inhalational corticosteroids are recommended as first-line therapy in mild, moderate, and severe persistent asthma[2], once the symptoms are stabilized, "stepping down" of steroids is recommended to minimize their unwanted effects with the addition of a second medication with a complimentary mechanism of action.[5-7]

Montelukast, a specific leukotriene receptor antagonist (LTRA), provides clinical benefit to patients with chronic asthma with a once-daily, oral administration.8 Montelukast blocks the interaction of cysteinyl leukotrienes with their receptors, there by inhibiting one of the inflammatory pathways in the pathogenesis of asthma. Since montelukast attenuates leukotriene-mediated effects, combination therapy with montelukast and inhaled corticosteroids (ICSs) can be an alternative to increasing the ICS dose in patients inadequately controlled on ICS alone.[8-10] In this study, we have evaluated the moderate dose of fluticasone propionate with the combination of low dose fluticasone and montelukast once daily in moderate persistent asthma patients.

Materials and Methods

Patients: Fifty moderate persistent asthma patients (as per the GINA guideline)[11] aged between 18-60 years, non-smoker, who attended the Respiratory Medicine outpatient department at the Himalayan Institute of Medical Sciences, Dehradun, from Jan. 2008 to Dec. 2008 were included in the study. Exclusion criteria were (a) age <18 years or >60 years, (b) patients having respiratory conditions other

than asthma, (c) smokers, (d) urgent medical care received for asthma, (e) oral corticosteroid use, (f) use of additional asthma medication and hospitalization during run-in period, (g) pregnancy, (h) lactation or (i) any other chronic systemic illness. The study was approved by the institutional ethics/research committee and written informed consent was taken from all the patients after the full explanation of study protocol.

Study Design: It was an open labelled comparative study with a 4 week run-in period to stabilize and familiarize the patients with study protocol. During the run-in period patients received fluticasone propionate 250µg twice daily, patients whose asthma was well controlled after 4 weeks of initial treatment were assigned for the study. After run-in period (-4week to 0 week) patients were divided in two groups: (i) Group I (n=25): Fluticasone 250 µg twice daily; and (ii) Group II (n=25): Fluticasone 125 µg twice daily plus Montelukast 10mg in night. Patients were observed fortnightly for 4 weeks and there after once every 4 weeks for another 8 weeks. Spirometry; FEV1% was done at enrolment (-4 week), at randomization (0 week) and at 12 week. PEFR% was done at -4, 0, 2, 4, 8 and 12 weeks. Absolute eosinophil counts (AEC) was done at -4 week and at 12 weeks. Routine investigations: Hb, TLC, DLC, ESR, blood sugar, chest X-Ray (PA view) were done at enrolment. The primary outcome measure were FEV1%, PEFR%, asthma symptoms (as per ACS score and additional medication use were recorded from patients daily diary)[12] and score related to QOL of patients. Asthma exacerbation and adverse effect to the medication were secondary end points. 12 week study period was decided on the basis previous studies showing maximum improvement by 4 week of intervention and keeping in mind the compliance of patients.[11,13]

The overall improvement in asthma quality of life (AQOL) was assessed by AQOL questionnaire by comparing the AQOL after the completion of study and AQOL before the initiation of study.[14] A check list was used to record side-effects and any adverse events experienced by the patients. The cost-effectiveness was measured by the ratio of direct cost of medication to outcome. The outcome was measured by difference in quality of life score before the initiation of the treatment and after the completion of treatment.

Cost Effective = Direct medication cost over 12 weeks / (AQLQ score after the completion – AQLQ before initiation of treatment)

Statistical Analysis: The treatment groups were compared and results analyzed by two tailed paired't' test. Values less < 0.05 were considered to be significant.

Results

Forty six of fifty enrolled patients completed the study. Four patients (two patients from each groups) were lost to follow up. Baseline characteristics and measures of asthma severity were similar in both the groups as shown in table 1. Results and observations relating to efficacy were assessed by Spirometry (FEV1%, PEFR%), ACS questionnaire scores and AQOL questionnaire score. Safety profile was assessed by noting the adverse events reported during the study. All results were expressed as Mean ± S.E for small group comparisons.

Table 1: Baseline characteristics of the patients

Parameter	Group I (FP)	Group II (M + FP-LD)
Age (18-60 years) (Mean ±SE) in Years	35.5 ± 3.97	27.0 ± 3.13
Average age at asthma onset (Mean ± SE) in Years	27.8 ± 3.81	19.5 ± 3.6
Average duration of illness (Mean ± SE) in Years	7.8 ± 2.15	4.5 ± 1.36
Frequency of exacerbation per month (Mean ± SE)	1.55 ± 0.07	1.47 ± 0.09
Daily inhaled corticosteroids (%)	12	17
Daily oral theophylline or salbutamol (%)	60	49
Combination therapy (%)	35	40
Unable to give proper drug history (%)	25	31
Using asthma medication daily (%)	21	18

FP: Fluticasone propionate; M + FP-LD: Montelukast + Low dose Fluticasone propionate

Table-2: Primary outcome measures

Lung Function	Groups	-4 week	0 week	12 week
FEV1%	**FP**	71.0 ± 1.69	89.3 ± 0.76$	91.2 ± 0.68*
	M + FP-LD	68.7 ± 1.51	88.6 ± 0.96$	91.1 ± 0.74*
PEFR%	**FP**	69.4 ± 1.53	89.9 ± 1.1$	95.5 ± 1.26**
	M + FP-LD	71.8 ± 2.18	90.14 ± 1.05$	93.9 ± 0.97*
AQOL score%	**FP**	37.0 ± 1.34	12.4 ± 1.56$	8.1 ± 0.64*
	M + FP-LD	39.7 ± 1.38	13.5 ± 1.50$	10.20 ± 0.66*
ASC score%	**FP**	13.6 ± 0.91	21.7 ± 0.50$	23.7 ± 0.21**
	M + FP-LD	11.8 ± 0.84	22.0 ± 0.47$	23.3 ± 0.30*

FP: Fluticasone propionate; M + FP-LD: Montelukast + Low dose Fluticasone propionate; $P < 0.001; as compared to – 4 week values in respective groups; *P < 0.05; **P<0.01; as compared to the 0 week values in respective groups.

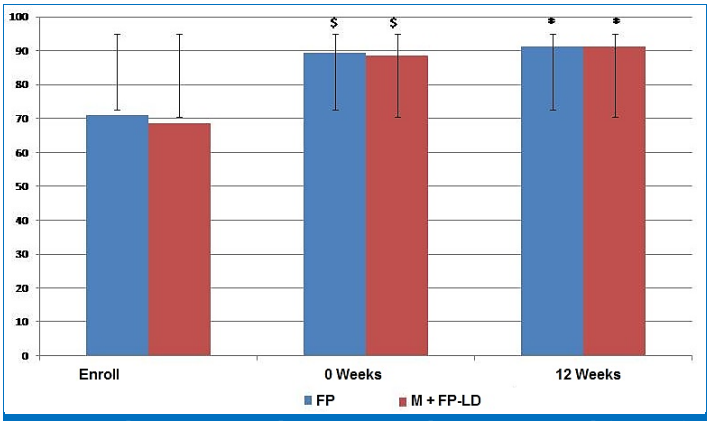

Figure-1: Change in Forced Expiratory Volume in 1 second (FEV1%)
(FP: Fluticasone propionate; M + FP-LD: Montelukast + Low dose Fluticasone propionate; $P < 0.001; as compared to – 4 week values in respective groups; *P < 0.05; **P<0.01; as compared to the 0 week values in respective groups)

Changes in all the respiratory parameters from the enrollment (-4 week) to the end (12 week) of the study for both the groups are listed in table 2 & figure 1-4. Improvement in all the respiratory parameters (FEV1%,

PEFR%, ACS score and AQOL questionnaire score) between - 4 week and 0 week were similar and highly significant ($p<0.001$) in both groups, and significant ($p<0.05$) improvement in all the respiratory parameters (FEV1%, PEFR%, ACS score and AQOL questionnaire score) were observed between 0 week and 12 week in both the groups. Efficacy parameters were improved substantially in both the study groups from – 4 to 0 week and further improvement was observed in both the group throughout the study period. The normal range of absolute eosinophil counts (AEC) is between 0-350/cumm Patients with AEC >350/cumm were 15 (30%) at the beginning of the study and 3 (6%) at 12 week. It shows that the AEC has a correlation with the disease severity and symptoms.

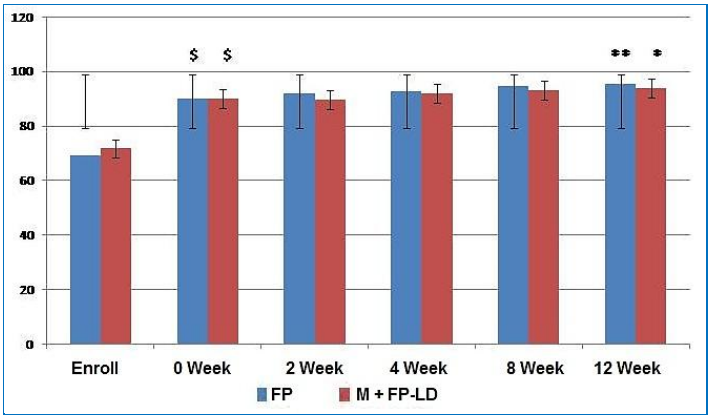

Figure-2: Change in Peak Expiratory Flow Rate (PEFR%) (FP: Fluticasone propionate; M + FP-LD: Montelukast + Low dose Fluticasone propionate; $P < 0.001; as compared to – 4 week values in respective groups; *P < 0.05; **P<0.01; as compared to the 0 week values in respective groups)

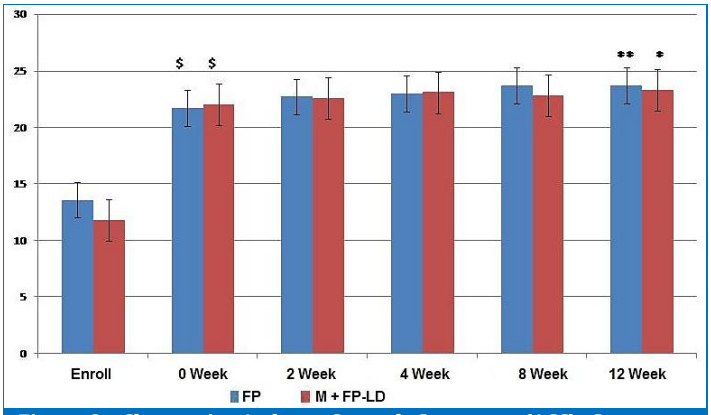

Figure-3: Change in Asthma Control Symptom (ACS) Score (FP: Fluticasone propionate; M + FP-LD: Montelukast + Low dose Fluticasone propionate; $P < 0.001; as compared to – 4 week values in respective groups; *P < 0.05; **P<0.01; as compared to the 0 week values in respective groups)

The most common adverse effects observed during the study were throat irritation, tiredness, GI disturbance and increase in appetite. The adverse effects observed were mild and nullify after 3-4 weeks, showed comparable incidence between the groups, do not required any medical intervention or withdrawal from the study. The direct cost of study drug in both group for 12 week of study period were approximately ₹ 1080 in group I and ₹1530 in group II respectively. The costs of rescue medication and other additional drugs used (antibiotics, anti-allergics, cough suppressants, etc.) over the study period in different groups are similar and does not have any significant affect as per the cost is concerned in our study.

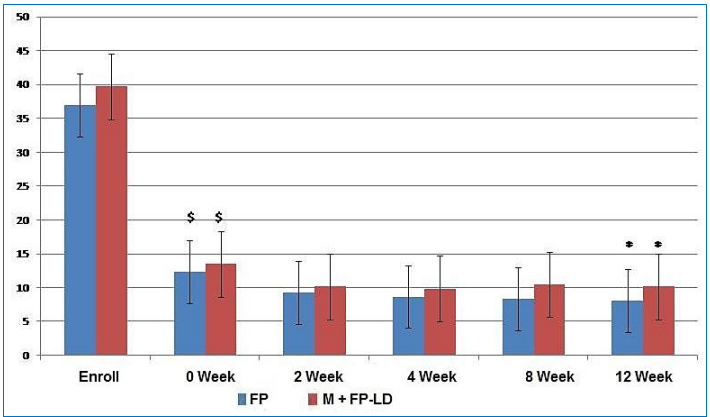

Figure-4: Change in Asthma Quality of Life (AQoL) Score (FP: Fluticasone propionate; M + FP-LD: Montelukast + Low dose Fluticasone propionate; $P < 0.001; as compared to – 4 week values in respective groups; *P < 0.05; **P<0.01; as compared to the 0 week values in respective groups)

Discussion

Treatment guidelines for asthma recommend the use of inhaled corticosteroids (ICS) as first line therapy for persistent asthma of all severities.[11,15] When asthma control has been achieved, the guidelines further recommend the "stepping down" of therapy to minimize the adverse effects of medication. Most studies of stepping down therapy involve patients with moderate or severe persistent asthma.[15]

In present study comparative evaluation of moderate dose of ICS fluticasone propionate with combination of low dose ICS fluticasone propionate and motelukast has been done as stepping down therapy, in moderate persistent asthma patients. In this study montelukast in combination with low dose fluticasone improved lung functions (FEV1%, PEFR%), asthma symptoms and QOL significantly, this is comparable to previous studies.[16-20] Since inhaled or oral corticosteroids have not been shown to attenuate leukotriene production in vivo[21], therefore, a leukotriene receptor antagonist in combination with inhaled corticosteroid may confer additional benefits and could be the best combination. Ducharme et al.[22] did a systematic review of 27 trials concluded that the addition of montelukast to add-on therapy to inhaled corticosteroids brings modest improvement in lung function. While in "stepping down" therapy addition of anti-leukotrienes is associated with superior asthma control after glucocorticoid tapering. Price et al.[18] have performed a randomized controlled trial of montelukast (10 mg) plus inhaled budesonide (800 µg /day) versus a double dose of

inhaled budesonide (1,600 µg /day) in adult asthma patients and concluded that addition of montelukast to inhaled corticosteroids is an effective and well-tolerated alternative to doubling the dose of inhaled corticosteroid in adult patients with persistent moderate asthma. There were significantly fewer investigator diagnosed respiratory adverse events in the montelukast plus budesonide group than in the budesonide 1600 µg group (11.6% v 16.6% of patients, $p<0.05$). In the montelukast plus budesonide group 166 patients (37.1%) experienced an adverse event compared with 182 patients (41.3%) in the budesonide 1600 µg group. The most common adverse events were upper respiratory infection, asthma worsening, and headache, pointing towards the adverse events precipitated by increased dose of corticosteroid mainly. From the above studies it is evident that montelukast in combination with low dose fluticasone is equally effective, safer and non- inferior to moderate dose fluticasone, it can be a better alternative to medium dose fluticasone in patients with moderate persistent asthma on long term maintenance therapy, keeping in mind adverse effects profile of corticosteroids.

Conclusion

Inhalational corticosteroid (ICS) fluticasone in medium dose and combination of low dose fluticasone with montelukast are equally effective in reducing asthma symptoms, improving lung functions and quality of life (QOL). Addition of montelukast to low dose fluticasone is non-inferior to the medium dose fluticasone. Incidences of adverse effects observed were less in combination therapy. Both groups showed equal efficacy in improving asthma symptoms; larger studies are indicated to substantiate the above results.

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