MONTELUKAST AS ADD-ON THERAPY TO INHALED BECLOMETHASONE IN PERSISTENT BRONCHIAL ASTHMA

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ABSTRACT

Objective: To evaluate the efficacy of Montelukast as add-on therapy in moderate persistent asthma with inadequate control on high dose inhaled beclomethasone.

Study Design: A quasi experimental study.

Place and Duration of Study: The study is carried out at the Combined Military Hospital Multan, from 1st Nov 2006 to 30th May 2007.

Patients and Methods: One hundred nonsmoking symptomatic asthmatics with one year history of moderate persistent bronchial asthma being treated with high dose inhaled beclomethasone dipropionate for at least 6 weeks before the study were selected as per inclusion criteria. Group-I (47 cases) was given inhaled beclomethasone (1000 µg daily in two divided doses) alone for 12 weeks. While Group-II (48 cases) received both inhaled beclomethasone (1000ug daily in two divided doses) and Montelukast Sodium 10 mg at bed time for 12 weeks. Seven-point global evaluation score and Pulmonary function test (PFTs) were done at 0, 6 and 12 weeks; and the need for use of rescue β2-agonist was also calculated in both groups.

Results: Mean age of patients was 29.30 years (SD±7.04) with 64.22% males. There was significant difference in episodes of dyspnea and wheeze among group I and group II at 6 weeks while all four parameters including cough and nocturnal awakenings were significantly less at 12 weeks in group II. Similar comparative improvement in mean FEV1 was seen at 12 weeks in group II. Combined therapy also reduced the use of rescue inhaled β2-agonist treatment.

Conclusion: Montelukast sodium as add-on therapy to high dose inhaled beclomethasone provides significant complementary clinical benefits in symptomatic moderate persistent asthmatics.

Keywords: Persistent Bronchial Asthma, Montelukast, Leukotriene Antagonists.

INTRODUCTION

Bronchial asthma afflicts about 300 million people worldwide [1] with major health care and financial burden due to uncontrolled disease [2]. Asthma is a chronic inflammatory disorder involving an interaction of many cell types and multiple mediators within the airways that eventually result in the characteristic pathophysiological features of the disease [3]. Among varied inflammatory mediators, cysteinyl leukotrienes (CysLTs) released from mast cells, eosinophils and basophils lead to bronchoconstriction, increased vascular permeability and mucus secretion3, proliferation of smooth muscle cells and fibroblasts [4]. They attract / activate inflammatory cells in the airways of asthmatics [3] CysLTs are only mediators whose inhibition has been specifically associated with an improvement in lung function and asthma symptoms [5]. Inhaled corticosteroids (ICS) affect many inflammatory pathways in asthma but have little impact on CysLTs [6,7]. This may partly explain persistent airway inflammation during chronic ICS treatment and inadequate asthma control in some patients.

Current guidelines recommend ICS as the first line controller therapy in persistent asthma with add-on therapy with a long-acting β2-agonist (LABA) or a leukotriene receptor antagonist (LTR) [3]. In this regard, addition of a LABA to existing ICS therapy

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leads to a more effective control than addition of LTR [8,9]. However patient adherence to once-daily oral controller medication like montelukast is superior to inhaled controller medications including ICS and LABA in both children and adults [10.11]. Montelukast, a CysLT1 receptor antagonist, reduces airway eosinophilic inflammation in patients with chronic asthma [12] and attenuates early and late airway responses to allergen and allergen-induced sputum eosinophilia in asthmatics [13]. Therefore, Montelukast has been shown to be specially beneficial in asthmatics with allergic rhinitis [14]. Complementary anti-inflammatory effects of montelukast and ICS have been shown in previous studies in adults [15,16] and children [17,18] with improved lung functions; reduced asthma symptoms, rescue β2- agonist use and asthma exacerbations in persistent asthma. However, in a few studies, add-on therapy with montelukast did not improve symptoms, lung function, or rescue bronchodilator use in adults with inadequate control on ICS [19].

The objective of this study was to evaluate the efficacy of Montelukast Sodium as add-on therapy in patients with moderate persistent asthma with inadequate control on high dose inhaled beclomethasone dipropionate.

PATIENTS AND METHODS

This quasi experimental study was carried out at Combined Military Hospital Multan, from 1st Nov 2006 to 30th May 2007. One hundered adults, 15-45 yrs of age, of both genders reporting to out patient medical deptt were sequentially enrolled. Only nonsmoking symptomatic asthmatics with one year history of persistent bronchial asthma treated with 1000ug/day of inhaled beclomethasone dipropionate for at least 6 weeks before the study were eligible for participation. Patients with upper respiratory infection within last 3 weeks, those with respiratory disorders other than asthma like ILD, COPD, or pulmonary tuberculosis; patients with atopic dermatitis, allergic rhinitis, nasal polyps, and predominant exercise induced asthma were excluded. Patients taking oral / parenteral corticosteroids within last one month; cromolyn or nedocromil within last two weeks; β2-agonists (oral or long-acting inhaled), anticholinergic agents, and theophylline (oral and intravenous) within last one week were excluded or were asked to stop medications before inclusion (if possible). Inhaled short acting β2-agonists and anti-allergics were allowed as needed during the study.

At baseline, a detailed history about cough, dyspnea, wheeze, and night awakenings was noted. Clinical examination included full respiratory, cardiac and relevant systemic assessment. PFTs were performed to document an FEV1 of 60-80% of predicted with reversible airway obstruction (an increment of at least 15% in FEV1 after salbutamol MDI use). Electrocardiography and chest radiograph were performed to exclude cardiac and lung parenchymal disorders. Patients were divided in two equal groups by random allocation using random number table.

Group-I was given inhaled steroids i.e. beclomethasone in the dose of 1000 µg daily in two divided doses alone for 12 weeks. Group-II received both inhaled beclomethasone 1000ug daily in two divided doses and Montelukast Sodium 10 mg at bed time for 12 weeks.

In both groups, objective assessment of symptoms of cough, dyspnoea, wheeze and frequency of night awakenings was made at baseline, 6 and 12 weeks visit 7-point global evaluation score(0=very much better, 1=much better, 2=better, 3=no change, 4=worse, 5=much worse, 6=very much worse). Similarly, PFTs were repeated at 6 and 12 weeks. Also the need for use of reliever/ rescue treatment was calculated in percentage in both the groups. The percentage improvement in FEV1 in both the study groups was calculated along with objective improvement in cough, dyspnoea, wheeze and decrease in the frequency of night

awakenings through 7-point global evaluation score and was compared with each other and thus the conclusion regarding better treatment modality was arrived. Compliance was enhanced by providing of educational material, patient motivation and involving household members into the study induction interviews. Written informed consent was obtained from each patient. Correct use of inhalers was ensured on pre-study visits and cases were only included after 6 weeks of correct inhaler use. Patients were also briefed about various side effect profiles of ICS and LTR's.

All the data was analyzed on computer on using SPSS program version 10.0. T-test was applied for the pre-study FEV1 values with the post-study values for significance. Qualitative variables like gender and the need for use of reliever/rescue treatment were described by frequencies and percentages and chi square test was applied to determine the significance. The Independent-Samples T Test was applied on the values of FEV1 obtained at the baseline, at 6 weeks and at 12 weeks of the study to assess the significance of add-on therapy with montelukast sodium.

RESULTS

One hundred patients who fulfilled the study induction protocol were included but results of 95 are included as 5 patients lost to follow up. A total of 64.22 % were males with mean age of 29.30 years (SD ± 7.04) for all cases. The age, gender and baseline average FEV1 at baseline in group I and group II were comparable as are shown in (table-1). Ninety five percent of our cases completed the study. Four (two from each group I and II) patients were lost to follow up and one patient from gp I was excluded due to noncompliance with medication (due to marked dyspeptic symptoms).

The values of mean FEV1 in Group I and Group II at 0 week, 6 weeks and 12 weeks are depicted in figure. The difference in mean FEV1 in Group I and Group II at 6 weeks was not statistically significant but it was found to be statistically significant at 12 weeks as shown in (table-2).

There was difference in episodes of dyspnea and wheeze in group II at 6 weeks as compared to group I (2.38 +/- 0.96 vs 2.80 +/- 0.89; p = 0.013 for dyspnea and 2.65 +/- 1.23 vs 3.06 +/- 0.92; p = 0.031 for wheeze) and it was statistically significant. However no statistically significant difference was noted in the episodes of cough (2.73 +/- 0.71 vs 2.94 +/- 0.77; p = 0.083) and night awakenings (2.50 +/- 1.17 vs 2.69 +/- 1.06; p = 0.197) among Gp 1 and Gp II at 6 weeks. At 12 weeks, there was significant difference in all the four parameters i.e. cough (2.09 +/- 0.65 vs 2.48 +/- 0.71; p = 0.003), dyspnea (1.89 +/- 0.79 vs 2.38 +/- 0.73; p = 0.001), wheeze (2.00 +/- 1.06 vs 2.60 +/- 0.79; p = 0.001) and frequency of night awakenings (1.55 +/- 1.00 vs 2.21 +/- 0.97; p = 0.001) in group II as compared to group I, as shown in (table-3).

The need for use of rescue inhaled β2-agonist treatment was seen in 14 (28%) patients in group I as compared to 5 (10%) in group II indicating that the combined therapy with ICS and montelukast reduces the use of rescue medicine (p<0.05).

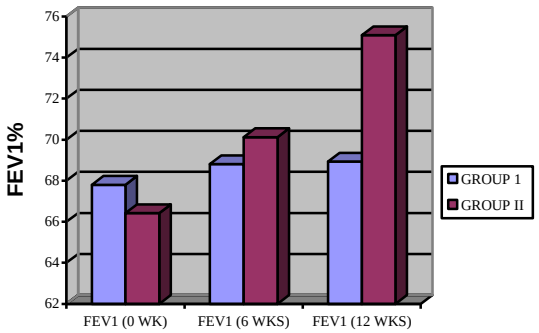

Fig: Mean FEV_1 Values of study group I & II at O, 6 and 12 weeks

DISCUSSION

Asthma control remains elusive in approximately 25% cases of persistent asthma despite guideline based management strategies [20]. In the present study, Montelukast Sodium has been found to improve the subjective as well as objective asthma control measures as assessed by 7-point global scoring system, FEV1 and rescue inhaled β2-agonist use, respectively. Similar results were achieved by Baumgartner and

colleagues on addition of montelukast to low dose ICS in adults [21] Montelukast as add-on to inhaled budesonide was assessed to be as effective and well tolerated alternative to doubling the dose of inhaled budesonide in adult asthmatics with inadequate control [22].

Table-1: Baseline characteristics of patients

Characters	Group I (N = 47)	Group II (N = 48)	P values	Total(N = 95)
Age (Yrs mean ±SD)	29.44±6.68	29.16±7.40	0.832	29.30±7.04
Male sex	29 (61.72%)	32 (66.66%)	0.216	61 (64.22%)
Female sex	18 (38.27%)	16 (33.33%)	0.193	34 (35.77%)
FEV1% of predicted (mean ± SD)	67.80 ± 9.38	66.42 ± 10.21	0.823	67.11 ± 9.79

Table-2: Mean and P-Values of FEV1 in Group I and Group II

Variable	Mean Values						P-value	
	At 0 week		At 6 weeks		At 12 weeks			
	Gp I	Gp II	Gp I	Gp II	Gp I	Gp II	06 wks	12 wks
FEV_1% of predicted (mean ± SD)	67.80 ± 9.38	66.42 ± 10.21	68.81 ± 11.23	70.12 ± 10.93	68.93 ± 9.78	75.09 ± 9.98	0.097	0.000

Table-3: Frequencies and P-Values of other study variables

Variables (frequencies)	At 6 wks	At 6 wks	p value	At 12 wks	At 12 wks	p value
	Group I	Group II	06 wks	Group I	Group II	12 wks
Cough	2.94	2.73	0.083	2.48	2.09	0.003
Dyspnea	2.80	2.38	0.013	2.38	1.89	0.001
Wheeze	3.06	2.65	0.031	2.60	2.00	0.001
Frequency of night awakenings	2.69	2.50	0.197	2.21	1.55	0.001

In the present study, improvement in dyspnea and wheeze was documented earlier as compared to other response parameters. These results are consistent with other studies where subjective measures or indices of inflammation were found to be more sensitive to the beneficial effects of add-on leukotriene modifier than lung function measurements [23]. Montelukast has been shown to be moderately effective in reducing the dose of ICS as demonstrated by Tohda and colleagues in a study of moderate-to-severe well controlled asthmatics on high dose inhaled beclometasone dipropionate [24]. Similar results were achieved in another study by Riccioni and colleagues on mild-to-moderate persistent asthma patients [25]. As our study also showed better control of asthma in the group II with use of Montelukast on the same dose of ICS; the ICS dose may be reduced in patients using ICS with montelukast without any worsening of the asthma. As regards use of LTR's in acute exacerbations, both oral Zafirlukast and I/V Motelukst have been proven beneficial [26,27].

Use of LTR's / montelukast as monotherapy in stable mild to moderate persistent asthma has shown to improve FEV1 (10-15%) and distal airways air-trapping; reduce daytime and nighttime asthma symptoms and thus improve asthma-specific quality of life with reduction in the need for rescue beta-agonist use and frequency of asthma exacerbations [28,29]. No evidence of tolerance to these beneficial effects has been noted during treatment for periods up to two years with better compliance on oral medications [30]. Recently, montelukast has also been shown to significantly attenuate myofibroblast accumulation and may be useful in preventing airway remodeling in asthmatics [14].

It has been observed that some of the patients of asthma are poorly controlled on ICS even in high doses [31]. More so; most of the benefit from ICS is achieved in adults at relatively low doses, equivalent to 400 µg of Budesonide or 500 µg of Beclomethasone dipropionate per day. Increasing to higher

doses provides little further benefit in terms of asthma control but increases the risk of side effects [32]. This prospective study confirmed observation from previous trials that montelukast sodium provides additional clinical benefits in symptomatic persistent asthma patients using constant doses of inhaled corticosteroids [33].

Our study has a few limitations. Firstly, group I has not been given placebo tablets to moderate the tablet intake effect of montelukast in group II on subjective asthma improvement parameters. Secondly, we have not implied genotypic markers and biomarkers associated with better LTR response although randomization has lessened this possibility. Recently, pharmacogenomics in asthma has documented heterogenous response to β2-agonist, ICS and LTR's [34,35]. As regards LTR, single nucleotide polymorphism (SNP) in Cysltr 1 receptor has been noted to be associated with allergic phenotype and thus better LTR response [34]. A similar SNP (LTC45) is associated with better Zafirlukast response [35]. Thirdly, NO, sputum eosinophil counts and histopathological evidence of attenuation of eosinophilic inflammatory response have not been documented to support the derived benefits in clinical and lung function parameters. Fourthly, this study was conducted on a small sample of persistent asthma cases, large-scale studies of similar nature are required to assess the effects of combined therapy with ICS and Montelukast on our adult asthmatics.

CONCLUSION

Montelukast sodium as add-on therapy to high dose inhaled beclomethasone provides significant complementary clinical benefits in symptomatic moderate persistent asthmatics and is well tolerated.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy 2004; 59:469-78
2. Navarro RP, Schaecher KL, Ricce GK. Asthma management guidelines: Updates, advances, and new options. J Manag Care Pharm. 2007; 13: S3-S11.
3. National Asthma Education and Prevention Program. Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD. National Heart, Lung and Blood Institute 2007. (NIH publication no.08-4051). Full text available online:www.nhlbi.nih.gov/guidelines / asthma / asthgdln.htm (Accessed March, 20 2008).
4. Espinosa K, Bosse Y, Stankova J, Rola-Pleszczynski M. CysLT1 receptor up regulation by TGF-beta and IL-13 is associated with bronchial smooth muscle cell proliferation in response to LTD4. J Allergy Clin Immunol 2003; 11:1032-40.
5. Leff AR. Regulation of leukotrienes in the management of asthma: biology and clinical trherapy. Ann Rev Med 2001; 52:1-14.
6. Gyllfors P, Dahlen SE, Kumlin M, Larsson K, Dahlen B. Bronchial responsiveness to leukotriene D4 is resistant to inhaled fluticasone propionate. J Allergy Clin Immunol 2006; 118:78-83.
7. Vachier I, Kumlin M, Dahlen SE. High levels of urinary leukotriene E4 excretion in steroid treated patients with severe asthma. Respir Med 2003; 97: 1225.
8. Ram F, Cates C, Ducharme F. Long-acting β2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev 2005; 1.
9. Pavord I, Woodcock A, Parker D, Rice L. SOLTA Study Group. Salmetrol plus fluticasone propionate versus fluticasone plus Montelukast: a randomized controlled trial investigating the effects on airway inflammation in asthma. Respiratory Research 2007; 8:67.
10. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, Stanford RH, Ryskina KL, Legorreta AP. Adherence to asthma controller medication regimens. Respir Med 2005; 99: 1263-7.
11. Bukstein DA, Luskin AT, Bernstein A. "Real-world" effectiveness of daily controller medicine in children with mild persistent asthma. Ann Allergy Asthma Immunol 2003; 90:543.
12. Pizzichini E, Leff JA, Reiss TF, Hendeles L, Boulet LP, Wei LX, et al. Montelukast reduces airway inflammation in asthma: a randomized, controlled trial. Eur Respir J 1999; 14:12-18.
13. Kelly MM, Chakir J, Vethanayagam D, Boulet P, Laviolette M, Gauldie J, et al. Montelukast treatment attenuates the increase in myofibroblasts following low-dose allergen challenge. Chest. 2006; 130:741-53.
14. Virchow JC, Prasse A, Naya I, Summerton L, Harris A. The Zafirlukast Study Group. Zafirlukast Improves Asthma Control in Patients Receiving High-Dose Inhaled Corticosteroids. Am J Respir Crit Care Med 2000; 162:578-85.

15. Vaquerizo MJ, Casan P, Castillo J. CASIOPEA (Capacidad de Singulair Oral en la Prevencion de Exacerbaciones Asmaticas) Study Group. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. Thorax 2003; 58: 204-10.
16. Laviolette M, Malmstrom K, Lu S. Montelukast added to inhaled beclomethasone in treatment of asthma. Am J Respir Crit Care Med 1999;160:1862-8.
17. Simons FER, Villa JR, Lee BW. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. J Pediatr 2001; 138: 694-98.
18. Phipatanakul W, Greene C, Downes SJ, Cronin B, Eller TJ, Schneider LC et al. Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. Ann Allergy Asthma Immunol 2003; 9: 49-54.
19. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. Lancet 2001; 357.
20. Bateman ED, Boushey HA, Bousequet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining asthma control study. Am J Respir Crit Care Med 2004; 170: 836-44.
21. Baumgartner RA, Martinez G, Edelman JM, Rodriguez Gomez GG, Bernstein M, Bird S, et al. Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone. Eur Respir J. 2003; 21: 123-8.
22. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax 2003; 211-6.
23. Biernacki WA, Kharitonov SA, Biernacka HM, Barnes PJ. Effect of montelukast on exhaled leukotrienes and quality of life in asthmatic patients. Chest. 2005; 128: 1958-63.
24. Tohda Y, Fujimura M, Taniguchi H, Takagi K, Igarashi T, Yasuhara H, et al. Leukotriene receptor antagonist, montelukast, can reduce the need for inhaled steroid while maintaining the clinical stability of asthmatic patients. Clin Exp Allergy. 2002; 32: 1180-86.
25. Riccioni G, Vecchia RD, Castronuovo M, Ilio CD, D'Orazio N. Tapering dose of inhaled budesonide in subjects with mild-to-moderate persistent asthma treated with montelukast: a 16-week single-blind randomized study. Ann Clin Lab Sci. 2005; 3: 285-9.
26. Silverman RA, Nowak RM, Korenblat PE, Skobeloff E, Chen Y, Bonuccelli CM, et al. Zafirlukast treatment for acute asthma: evaluation in a randomized, double-blind, multicenter trial. Chest 2004; 12: 1480-89.
27. Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. Am J Respir Crit Care Med 2003; 167: 528-33.
28. Zeidler MR, Kleerup EC, Goldin JG, Kim HJ, Troung DA, Simmons MD, et al. Montelukast improves regional air-trapping due to small airways obstruction in asthma. Eur Respir J 2006; 27:307-15.
29. Kraft M, Cairns CB, Ellison MC, Pak J, Irvin C, Wenzel S. Improvements in distal lung function correlate with asthma symptoms after treatment with oral montelukast. Chest. 2006; 130: 1726-32.
30. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. Arch Intern Med 1994; 154: 1349-52.
31. Kamada AK, Szefler SJ, Martin RJ, Boushey HA, Chinchilli VM, Drazen JM, et al. Issues in the use of inhaled glucocorticoids. Am. J. Respir. Crit. Care Med.1996; 153: 1739-48.
32. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. Am J Med 1995; 98: 196-208.
33. Malmstrom KG, Rodriguez-Gomez, J Guerra, C Villaran, A Piñeiro, LX Wei, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. Ann. Intern. Med. 1999; 130: 487-95.
34 Zhang J, Pare PD, Sandford AJ. Recent advances in asthma genetics. Respiratory Research 2008; 9: 9921-29.
35 Morrow TJ. Implications of pharmacogenomics in the current and future treatment of asthma. J Manag Care Pharm 2007; 13: 497-505.