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Evaluations of Motelukast As Add On Therapy (Corticosteroid Sparing Effect) To Inhaled Cortocosteroids In Patients With Chronic Persistent Asthma

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Abstract

WHO recognizes asthma as a disease of major public importance and stimulates research in to the causes of asthma to develop new control strategies and treatment techniques. Inhaled corticosteroid (ICS) used as first line preventive therapy is associated with systemic adverse events. The aim of the study was to improve patient care and therapeutic benefits by including montelukast along with ICS. The corticosteroid sparing properties of montelukast was studied and the efficacy of concomitant montelukast was evident in test group with FEVI value (2.16vs1.73) with improvement in mean day time score and mean asthma free days and reduction in ß agonist use & mean asthma exacerbation days.

Key words:
Asthma, Montelucast, inhaled corticosteroids

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INTRODUCTION:

Asthma[1,2,3] is a chronic disease affecting the airways, which is a serious and a growing health problem. There[4,5] is no one symptom or physical characteristics or laboratory test that defines asthma. Rather asthma is recognized from a pattern of symptoms including wheeze, cough, chest tightness and dyspnoea; and it is confirmed by evidence of variable or reversible airflow obstructions.

Asthma can be found in almost every population in the world. According to WHO[1,5,11,12] between 100-150 million people around the globe – rougly equivalent to the population of the Russian federation – suffer from asthma and this number is increasing. Worldwide, deaths from this condition have reached over 180,000 annually. India[2,6,12] has an estimated 15-20 million asthmatics. In India, a rough estimate indicates a prevalence of between 10-15% in 5-11 year old children.

Leukotriene receptor antagonists[4,5,6,7] are an important new class of non steroidal anti-asthma therapy in that they are effective over a wide range of asthma severeity with a high Therapeutic index and are orally active. Montelukast (montelukast sodium) is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene cysLT, receptor. Cysteinyl leukotrienes and leukotriene receptor occupation have been correlated with pathophysiology of asthma, including airway edema, smoothmuscle contraction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. The corticosteroid sparing properties of montelukast[8,9,10,11,12] are important in that many of the long term adverse effects of inhaled corticosteroids are dose related. The aim of the present study was to ensure and improve patient care and benefit, taking into consideration of the alternative add on therapy in chronic asthma patients, there by reducing the adverse effects of steroids on prolonged use.

METHODOLOGY:

This study was conducted in a clinic in Madurai city owned by renowned pulmonologist and bronchocopist Dr. S. C. Vivekananthan after due Ethics Committee approval. The study was done in 4 phases and it was an open, non-comparative type of study. A total number of 59 patients were enrolled in the study after obtaining informed consent. The study has two arms, the test group and the control group. The study was conducted over a period of 6 months from July to December 2008. Prospective data was collected from the patients on 4 evaluation visits. Together with the data symptomatic changes and variation in PFT were also noted.

The test group were treated with budesonide, formoterol + montelukast 10 mg and the control group with budesonide plus formoterol alone for a period of 75 days. The dose of the steroid is tapered on 60th day of the trial and the efficacy parameters evaluated on the 75th day. The effect of drug was studied by two methods (i) Observational analysis (Symptomatic change) and (ii) Laboratory parameters (FEVI). The data were collected, compiled, analysed with statistical tools (SPSS – Microsoft Version 6).

RESULTS AND DISCUSSION:

During the present study, it was observed that about 40% of the patients coming to the clinic with chronic persistant asthma were between 31-45 years of age, and the rest belonged to other age group. Out of the study population 55.6% were females and 44.4% were males. It was also observed that 55.6% were free from any concomitant diseases. During the first 4 weeks, both the test and control group received budesonide, formoterol combination, a fixed dose of 400/800/1600 mcg/day with 6 mcg formoterol in a single rotahaler(foracort). It was observed that there was a reduction of asthma daytime/nocturnal symptoms and lung functions (FEVI). During the next 4 weeks

(visit-2). The drug montelukast (10mg) was added to the existing therapy in the test group.

On the 60th day (Visit-3) the dose of steroids was tapered to 50% in both groups but the dose of montelukast was maintained the same in the test group at the end of 15 days treatment periods, the patients were evaluated. The observations showed that the patients in the test group were stable

compared to their symptoms scores and FEVI values taken prior to dose tapering whereas the patients in the control group at the end of 15 days of dose tapering of steroids showed an increase in symptoms and decreased FEVI values compared to prior values. These observations points to the anti-inflammatory and bronchodilatory properties of montelukast. The mean values of each of the parameters both primary and secondary end points were compared at the end of total study period of 75 days. The results were promising and all the values were significant.

Patients receiving concomitant montelukast experienced a 6.43% reduction in mean asthma exacerbation days from baseline compared to 2.5% of the control group and the mean asthma free days was 6.45% Vs 2.51% increase from baseline in test and control respectively. Asthma exacerbation days and asthma free days are clinically relevant primary end points that reflect the extent of asthma control experienced by patients on a daily basis.

The need for β agonist reliever therapy was (84.45% Vs 73.94% reduction), noctarnal symptom score was (73.08% Vs 58.46% reduction), day time symptom score was (58.9% Vs 49% reduction) mean FEVI values was (24.9% Vs 24% increased). These improvements[66] occurred despite the improvement occurred due to steroid therapy, this points to the lack of effect of inhaled steroids on leukoterienes as well as the goals of asthma treatment according to international consensus guidelines. Asthma treatment should aim to reduce or eliminate chronic symptom and asthma exacerbations, minimize the need for β agonist rescue medication, permit normal activity levels and maintain a normal lung function.

This study is first of this kind to evaluate the steroid sparing effect of montelukast in the combination of budesonide – formoterol in India using asthma exacerbation days and asthma free days as primary end point.

The international consensus guidelines have proposed[13,14] LTRA as an alternative to long acting β agonist or both for use as concomitant treatment with ICS for patients with moderate persistant asthma. The NAEPP[7] guidelines propose LTRA as first line treatment for patients with mild persistant asthma.

The efficacy of concomitant montelukast was evident in both doses of 400 and 800 µg of budesomide used in the test group. The study has also shown the complementary activity of antileukotriene with inhaled budesomide in patients in test group compared to baseline FEVI value (2.16 Vs 1.73). Concomitant montelukast and ICS treatment produced additive effects on peripheral blood eosinophil counts with significantly lower counts than on corticosteroids alone which suggest that ICS and LTRA[8,9,10,11,12] may have complementary anti-inflammatory activity which may allow for tapering of ICS dose in stable patients. In two studies[15,16] montelukast with inhaled budesonide showed to be an effective and tolerated as double dose of inhaled budesonide.

CONCLUSION:

The study has shown that the concomitant administration of monteukast with budesonide in doses 400-1600 mcg/formoterol 6 mcg/day by rotahaler provides significant additional benefit and steroid sparing effect, improved/ maintenance of asthma control in the montelukast group(test) inspite of steroid dose tapering, is evident in the increased percentage of asthma free days, the decreased percentage of asthma exacerbation days and decreased daytime and nocturnal symptom scores and increased FEVI values.

Inhaled corticosteroids employed as first line preventive therapy for asthma, have a shallow dose response curve for antiasthmatic efficacy and a steeper curve for systemic adverse effects concerns about potential systemic adverse effect of ICS is important because of a tendency to prescribe higher doses when initiating treatment, along with a failure

to taper to the lowest effective maintenance dose. Even though ICS is the most commonly used controller medication but in terms of compliance it may limit the real world effectiveness especially in the elderly and pediatric patients. Long term use of ICS[1,3,17,18,19] predisposes patients to dose related adverse events including bone density, osteoporosis, cataracts, glaucoma, skin bruising, impaired growth in pre-pubertal children. Therefore therapeutic strategies of including the use of antileukotrienes to minimize the dose of ICS without compromising asthma control should be evaluated.

Asthmatic patients with a disease duration of atleast 3 months, daytime total asthma score of atleast 8 and one nocturnal awakenings or early morning awakening were included in the study. Patients with a history of allergic reactions to formoterol and patients who had emergency treatment for asthma within one month or hospitalization within 3 months prior to enrolment were excluded from the study. Data was collected from interview with the patient, case notes, prescription, treatment charts and laboratory date including PFT of adult patients.

Table No.1 BASELINE CHARACTERISTICS OF RANDOMIZED PATIENTS

CHARACTERISTICS	CONTROL (N = 21)	TEST (MONTELUKAST) (N = 24)
Mean age (SD) Range(years)	43.38(16.86) (15-14)	37.4(12.61) (15-59)
Sex(n)% Female Male Ex-Smokers	 11(52.4%) 10(47.6%) 6(28.57%)	 14(58.3%) 10(41.7%) 5(20.83%)
Mean Duration of Asthma Months (SD)	97.52(75.10)	66.91(55.7)
Mean FEVI	1.50(SD – 0.37)	1.73(SD – 0.31)
Mean FEVI%(SD)	62.65(3.62)	63.31(4.38)
Budesonide dose level 100-800 mg/day 801-1200 /day 1201-1600 /day	 20(95.24%) 0 1(4.76%)	 24(100%) 0 0
Mean Day time Asthma Score(SD)	10.04(1.37)	9.625(1.30)
Mean Nocturnal Asthma Score(SD)	3.9(0.59)	3.79(0.72)
Mean β agonist use(SD)	4.42(0.87)	4.95(0.72)
Mean % Asthma Exacerbation day	2.14(7.14%)	2.2(7.36%)
Mean % Asthma free days	41.78(92.85%)	41.68(92.63%)
Global Assessment Physician Patient	 3.14(0.36) 2.95(0.59)	 3.50(0.57) 3.17(0.38)

Table No.2: RESULTS OF EFFICACY END POINTS WITHOUT BASELINE VALUES

End Point	Control	Test	Effective Difference	P
Mean FEVI	1.86	2.16	0.3	0.022
Mean Daytime Score	5.12	3.96	1.16	0.000
Mean Nocturnal Asthma Score	1.62	1.02	0.6	0.003
Mean β Agonist	1.29	0.687	0.603	0.001
Mean Asthma exacerbation days (%)	2.09(4.64%)	0.42(0.93%)	1.67	0.000
Mean Asthma free days (%)	42.9(95.36%)	44.59(99.08%)	1.69	0.000
Global Assessment Physician Patient	 3.31 3.07	 2.98 2.79	 0.33 0.28	 0.000 0.014

REFERENCES

1) Malcon R. sear, Evidence Based Asthma Management, "Natural History and Epidemiology", B.C. Decker Inc., London, 2001, pp. 1-12.
2) National Heart, Lung and Blood Institute (NHLBI), 1985.
3) Richard A. Nicklas and Albert l. Sheffer, Asthma Management for New Millennium, "Guidelines for Asthma – Relating Local Needs and Global Initiatives", Adis International ltd., pp. 37-44.
4) Product Manual on Montelukast by Ranbaxy Labs, 2001
5) O.J.Dempers, Leukotriene Receptor Antagonist Therapy, Postgrad. Med J, December 2000; 76:767-773.
6) Lipworth, B.J., Leukotriene Receptor Antagonist, Lancet 1999; 353:57-62 (Medline).
7) Montelukast – Adis Drug evaluation, April 2000, 59: 891 – 928.
8) Kannesis, F., Richter, K., Janicki, S., Schlesis, M.B., Jorres, R.A and Magnussen, H., Dose Reduction of Inhaled Corticosteroids under concomitant medication with montelukast inpatients with Asthma, European Respiratory journal, November 2002, Vol. 20 No.5, pp. 1090 – 1097(8).
9) Tohda, K., Fujimura, M., Taniguchi, H., Takagi, K., Igrashi, T., Yashuhara, H., Takalashi, K., and Nakajima, S., Leukotriene Receptor Antagonist, Montelukast can reduce the need for inhaled steroids while maintaining the clinical Stability of Asthmatic patients, clinical and Experimental Allergy, August 2002, Vol. 32, No.8 pp.1180-1186(7).
10) David B. Price, m. B., Michael, Y., Rouleau, M.D. and Christopher, B., Use of Montelukast in Tapering Inhaled Corticosteroid Therapy: An open Label, 48 Week trial, Current Therapeutic Research, November 2001, Vol.62, Issue 11, pp. 743 – 755.
11) Shah, A.R., Which is more Steroid Sparing in Persistent bronchial Asthma? Montelukast or Theophylline, Journal of Allergy and Clinical Immunology, February 2004, Vol. 113, Issue 2, Supplement 1,pp. S34-S35.
12) Claes-goran lofdahl, Theodore F.Reiss, Jonathan A.Leff, Elliot Israel and Michel J.Noonan, Randomized Placebo Controlled Trial of Effect of a Leukotriene Receptor Antagonist, montelukast on Tapering Inhaled Corticosteroids in Asthmatic patients, BMJ, July 1999,319:87-90.
13) The British guidelines on asthma management 1995, Review and Position Statement, Thorax 1997;52(90001):S1-S2(February).
14) Riccioni,G.,ilio, C.D. and D'Orazio, An Update of the Leukotriene modulaters for the Treatment of Asthma , Expert Opinion on Investigational Drugs, July 2004, Vol.13,No.7,pp.763-776(14).
15) Price,D.B.,Hernandez, D.,Magyar, P., Fiterman, J., Bech, K.M.,James, I.G.,Konstantopoulos, S.,Rojas,R., Van Noored, J.A., Pons, M., Gilles, l.and Leff, J.A., Randomized Controlled Trial of Montelukast plus Inhaled Budesonide Versus Double Dose Inhaled Budesonide in Adult Patient with Asthma(COMPACT STUDY),Thorax 2003,58:211-216.
16) Yildirim,Z., Ozlu, T., Bulbul, Y. and Bayram, H., Addition of Montelukast Versus Double Dose of Inhaled Budesonide in moderate Persistent Asthma, Respirology , June 2004,Vol.9,No.2,pp.243-248(6).
17) William D. McConnel and Stephen T. Holgate, asthma, 4th Edition, the Definition of asthma: Its Relationship to other Chronic obstructive lung Diseases", Arnold Publishers, 2002, p. 1-32.
18) Roger Walker, Pathologic Basis of Disease, Stanley L. Robbins, 6th Edition, p.712.
19) Richard Hubbard and Anne Tattersfield, Inhaled Corticosteroids, Bone Mineral Density and fracture in older people, drugs and ageing, 2004,Vol.21,No.10,pp.631-638(8).