

## COMPARISON OF THERAPEUTIC VALUES BETWEEN LEUKOTRIENE RECEPTOR ANTAGONIST (MONTELUKAST) AND INHALED GLUCOCORTICOIDE (BECLOMETHASONE PROPIONATE) IN BRONCHIAL ASTHMA OF ADULTS

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### ABSTRACT

**Objective:** To compare therapeutic values between leukotriene receptor antagonists (Montelukast) and inhaled glucocorticoids (Beclomethasone) in naturally occurring bronchial asthma of adults.

**Methodology:** A total of 765 patients suffering from various respiratory disorders were examined. All of them were adults and belonged to the male gender. Comparison of therapeutic values between the administration of Montelukast and inhalation of Beclomethasone in naturally occurring bronchial asthma in adults was studied.

**Results:** Out of 765 patients examined, sixty (7.8%) were diagnosed to be asthmatics on the basis of characteristic symptoms, physical and clinical examinations and Lab tests. The patients had persistent cough, wheezing, chest tightness, suffocation and shortness of breath, anxiety and nocturnal paroxysms. They represented 36.6% businessmen, 28.3% textile workers, 18.3% teachers, 10% hospital employees and 6.6% students. All of them were hospitalized for two weeks in the Ali ward of the Divisional Headquarters (DHQ) hospital; Faisalabad. The first group of 30 patients selected randomly was treated for 8 weeks with Montelukast and the second group of the remaining 30 patients with inhalation of Beclomethasone for the same period. The enzyme, Alanin Transaminase (ALT) was found elevated in all the 30 patients treated with Montelukast ( $P < 0.001$ ). The Peak Expiratory Flow Rate (PEFR) of the patients treated with both Montelukast and Beclomethasone was measured. The mean values of PEFR values obtained with Montelukast differed favourably for the 1st and 3<sup>rd</sup> week ( $P < 0.05$ ) and relatively so during later weeks which was also statistically similar to that of Beclomethasone. The age of the patients appeared to remain uninfluenced with the protocols of the two medicines.

**Conclusions:** The treatment with Montelukast resulted in rise of the enzyme, ALT in all the asthmatic patients and their PEFR values showed more favorable results for the 1st and 3<sup>rd</sup> weeks and relatively so around 6<sup>th</sup> week and later which was statistically similar to that of Beclomethasone. The age of the patients showed no variations in PEFR values obtained with the two types of medication used.

**KEY WORDS:** Bronchial asthma, Montelukast, Beclomethasone.

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### INTRODUCTION

Asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, particularly, mast cells, eosinophils, T-lymphocytes, neutrophils and epithelial cells. The asthma syndrome

is characterized by variable obstruction to airflow, bronchial hyper-responsiveness and inflammation.<sup>1</sup> Leukotrienes are biologically active fatty acids derived from the oxidative metabolism of arachidonic acid. These are potent biochemical mediators that are released from mast cells, eosinophils and basophils. Leukotrienes work to contract airway smooth muscle, increase vascular permeability, mucus secretions and attract as well as activate inflammatory cells in the airways of patients with asthma.<sup>2</sup>

The action of Leukotrienes can be blocked through either of the two specific mechanisms: 1) inhibition of leukotriene production and, 2) antagonism of leukotriene binding to cellular receptors. Montelukast and Zafirlukast have been reported as leukotriene receptor antagonists of leukotriene D and E, which are components of slow reacting substance of anaphylaxis.<sup>3</sup> These drugs are not indicated for acute exacerbations but are recommended for prophylaxis and chronic treatment of asthma in adults and in children over 12 years of age. Leukotriene receptor inhibitors may also be used to reduce the low-dose regimens of corticosteroid inhalers.<sup>4</sup> The adverse reactions of Leukotriene inhibitors may appear in the form of headache, abdominal pain, nausea, dyspepsia, ALT elevation, myalgia and generalized pain.

Montelukast (Singulair) is an orally administered, selective cysteinyl leukotriene (CysLTI) receptor antagonist. The initial response after a single dose of administration of Montelukast occurs in three to four hours and the duration of action lasts for 24 hours. In clinical studies, Montelukast yields improvement in several asthma parameters, which include improved Forced Expiratory Volume (FEV), day and night, symptoms and reduction in the use of beta-antagonists.<sup>5</sup> Montelukast has also been demonstrated to provide significant protection against exercise-induced asthma. The present study was designed to compare the therapeutic effects of oral administration of Monteleukast(MSD), a potent cysteinyl leukotriene receptor antagonist with inhaled glucocorticoids, Beclomethasone propionate

(Glaxo Wellcome) in the treatment of naturally occurring bronchial asthma<sup>6</sup> in adults. The study was not sponsored by any pharmaceutical company, and this data was derived from dissertation submitted as partial requirement for FCPS.

## METHODOLOGY

The patients for this study were selected from among those coming for treatment to the Out Patient Department, held regularly three days a week, and also from those referred to Ali Ward, the Medical Unit IV of the Divisional Headquarters (DHQ) Hospital, Punjab Medical College, Faisalabad. This medical unit comprises of 70 beds and deals with emergencies round the clock. All the patients were male as the Ali Ward (DHQ Hospital) where the study was conducted, admits only male patients. The DHQ hospital is centrally located and extends medical cover to inhabitants of Faisalabad, educational institutes, inmates of three jails located in this city as well as adjoining areas. Of a total number of 765 patients having various respiratory disorders, attending DHQ Hospital, 60 asthmatic patients selected randomly were hospitalized for two weeks.

The asthmatic patients were categorized into mild, moderate and severe according to the reversibility of bronchospasm and the number of attacks during study period. They were having persistent symptoms of wheezing, chest tightness, suffocation, cough, shortness of breath and anxiety. These exacerbations affected their daily activities accompanied with anorexia, loss of weight, weakness and lassitude and lack of concentration. Paroxysms of nocturnal asthma forcing the patients to sit on their beds were a characteristic feature. Physical and clinical examinations of all the asthmatic patients including recording of pulse and respiratory rates, blood pressure, clubbing, cyanosis, pallor, jaundice and oedema of lower extremities, when present were observed. There were no chest or spinal deformity/symptoms of respiratory failure in any of the patients. The patients were also trained well

to use peak flow meters and inhalers with a spacer device meters before and during treatment.

The tablet Montelukast (Singulair, MSD) 10mg. was administered orally during each night for eight weeks to the randomly selected first group of 30 patients and ALT and PEFR values were recorded once before and later at weekly intervals for 8 weeks during treatment. The second group of remaining 30 patients was allowed inhalation with glucocorticoids, Beclomethasone propionate (Glaxo Wellcome) 250Hg and PEFR values were determined once before and later at weekly intervals during treatment. No other drug to any of the patient, under observation, was allowed to be taken other than rescue short acting B2-agonists during this study.

#### Inclusion Criteria:

1. From among a large number of patients showing respiratory disorders, 60 patients were diagnosed to be asthmatic on the basis of physical and clinical examinations and by measuring PEFR values, using Peak Exploratory Flow Meter from Bayer Pharmaceuticals.
2. All patients were adults above 40 years of age and belonged to the male gender.

#### Exclusion Criteria:

1. Smokers
2. Patients showing clinical signs of other diseases including diabetes mellitus, ischaemic heart disease, pulmonary tuberculosis, chronic liver disease and rheumatoid arthritis were excluded and no patient was either found dependent on any previous therapy.

*Measurement of ALT:* It was measured as described below:

1ml Buffered substrates having pH 7.4 was added into each of two large test tubes pipette and placed at 37°C in water bath for at least 5 minutes. Then 0.2ml of serum was added at an exact time to the first tube, mixed well and incubated at 37°C also for one hour. Then 0.2ml of Enza-trol was added at an exact time to the second tube, mixed well and incubated at 37°C exactly for one hour. After completion

of incubation period, 1ml of color developer was added to both tubes which were allowed to stand at room temperature for 20 minutes. After 20 minutes, 10ml of 0.4N NaOH was added to both tubes. Mixed and allowed to stand for at least five minutes at room temperature. It was read at wavelength specified for instrument being used. Adjust reading of water blank for 100 percent transmittance or zero optical density. Then from percent transmittance or optical density were read as units of ALT per milliliter from the curve.

*Statistical Analysis:* The data on ALT level before and during treatment for 8 weeks with Montelukast was analyzed with paired-t test using Minitab software<sup>8</sup> while the data on PEFR values of patients used Monteleukast and Beclomethasone was analyzed using a general linear model having medicines as variables and age of the patients and PEFR before treatment as co variables.

## RESULTS

This study was carried out for 8 weeks and of 765 patients having different respiratory disorders, 60 (7.8%) asthmatic patients were randomly selected. These patients showed difficult respiration, wheezing, chest tightness, persistent cough and nocturnal paroxysms. In the present study, the asthmatic patients were found to be mild (23), moderate (17) and severe (20) based on the reversibility of bronchospasm and the number of attacks during the study period. The average pulse and respiration rates in these patients were 78 and 15 per minute, respectively. Two of the patients appeared anaemic and another showed cyanosis. The average blood pressure was found to be 110/80mm/hg. There was no clinical evidence of clubbing, jaundice and oedema of lower extremities. The lymph nodes and thyroids were non-palpable and there was no jugular venous pressure, no deviation in the location of trachea and no apparent musculo-skeletal abnormalities. The occupation and lifestyle of all asthmatic patients (Table-I) were ascertained.

Table-I: Occupations, use of carpets and cohabitation with pets/ large animals

No. of patients	Percentage	Occupation	Use of carpets	Cohabitation
22	36.6	Businessman	Yes	Buffaloes & parakeets
04	6.6	Students	No	Parakeets and dog
06	10	Hospital employees	Yes	Buffaloes and dogs
17	28.3	Textile workers	Yes	Dog
11	18.3	Teachers	Yes	Buffalo

The present study showed highest number (36.6%) of asthmatics was businessmen, followed by textile workers (28.3%), school teachers (18.3%), hospital employees (10%) and students (6.6%). All asthmatic patients were found to be hypersensitive to seasonal variations and aeroallergens including pollen, dust, fumes and smoke.

*Treatment Trials:* Blood samples collected from first group of 30 patients treated with Montelukast before and during treatment for eight weeks were analyzed to determine alanine transaminase (ALT) level and the results are presented below:

Before treatment 25.10± 7.13  
 After treatment 27.63±7.82  
 (t=3.836, P<0.001)

A significant increase in ALT level was detected in patients treated with montelukast for 8 weeks. Blood values of peak exploratory flow rate (PEFR) of 30 patients each of first and second group, before and after giving montelukast and beclomethasone respectively for 8 weeks at weekly intervals were determined and results are presented in Fig-1.

Treatment of asthma both with tablet montelukast and inhalation of beclomethasone was continued for 8 weeks. The PEFR level with montelukast rose gradually for the first four weeks as compared to that of beclomethasone. In the 5<sup>th</sup> week, the level was almost equal with both the drugs and thereafter during 6<sup>th</sup>, 7<sup>th</sup> and 8<sup>th</sup> week, the level attained with beclomethasone was maintained and showed an upward trend as compared to that of montelukast Fig-1.

The PEFR values before treatment showed important variation source for readings and

there after the mean for 1<sup>st</sup> and 3<sup>rd</sup> week differed (P<0.05) in favour of Montelukast but for later weeks although, PEFR values for Montelukast were better but statistically similar to that of Beclomethasone. The age of the patients did not affect the response of the two medicines probably because it was not in a very wide range.

## DISCUSSION

Among diseases of the lungs, asthma is a chronic inflammatory condition of the lung airways that is characterized by an increased responsiveness of the bronchial tree to a multiplicity of stimuli. Clinically, there are paroxysms of cough, wheezing, chest tightness and cough were also observed in the present study. The airway narrowing that occurs in asthma is intermittent and variable so that complete remission can occur between the attacks although functional abnormality is detected with more sensitive tests.<sup>9,10</sup> In susceptible individuals, inflammation of the lung airways causes recurrent episodes of difficult respiration with acute exacerbations interposed with symptoms-free period. Most attacks are short-lived lasting for minutes to an hour<sup>11</sup> and the patient seems to recover after an attack.

The prevalence of asthma is related to geography, ethnicity and age of individuals.<sup>12</sup> Evidence is also accumulating on the prevalence of asthma to allergic diseases<sup>13,14</sup> in relation to culture and lifestyle than to genetic predisposition. Asthma occurs at all ages but predominantly in early life. About one-half of cases develop before age 10 and another one third occur before the age of 40. These reports corroborate with the present findings in which

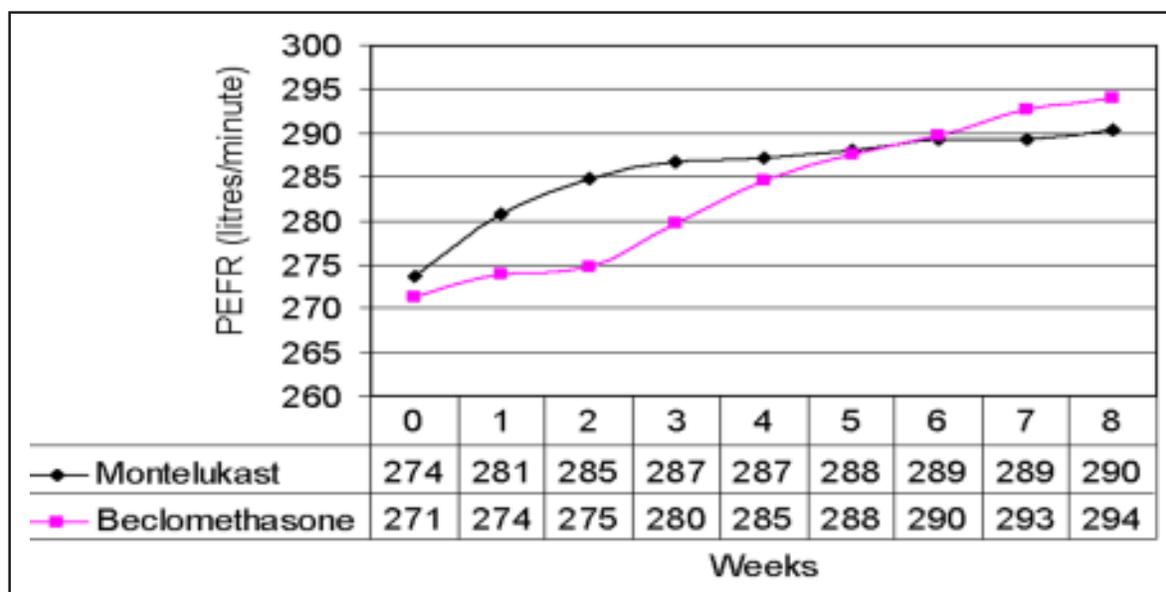


Figure-1: PEFR values for two drugs.

businessmen and textile workers showed highest incidence of asthma because of their profession and occupation associated with powerloom industry in Faisalabad. Factors that could cause increase in asthma prevalence include tobacco smoke, alteration in diet, and increased exposure to allergens, environmental pollution and occupational sensitizing agents.<sup>9,15</sup>

Studies of occupational asthma suggest that a higher percentage up to 20% of the people become asthmatic if exposed to potential sensitizers. The most important risk factors for the development of asthma are atopy, cigarette smoke exposure and childhood bronchitis.<sup>16</sup> Allergens diagnosed by allergy evaluation include skin testing and negative response to a battery of appropriately selected allergens strongly suggests the absence of an allergic component. A positive response indicates only potential allergic reactivity to the tested allergens. The clinical significance of results is determined by correlating them with pattern of symptoms and with environmental exposures.<sup>4</sup>

Choudat<sup>17</sup> reported six major categories of exposure which should be considered in taking history of asthma: (1) animals, shellfish, fish or arthropods: (2) wood, plants and vegetables:

(3) enzymes and pharmaceutical agents: (4) chemicals (solder fluxes and dyes) (5) metals and (6) dusts, fumes and gases. In the present study, among 60 asthmatic patients, businessman represented highest (36.6%) number which could be due to their association with yarn and textile industry because Faisalabad is known for textile business. The next highest number of asthmatics was textile workers (28.3%) which further supplements our findings that inhalation of fibers, dyes and chemicals used in textile industry act as allergens to cause asthma. School teachers, students and hospital employees were found to be 18.3%, 10% and 6% asthmatic respectively. This reflects high level of pollution existing in Faisalabad. Cohabitation by keeping buffaloes, pets and parakeets in the house could be the additional source of aeroallergens to develop asthma.

Patients who have occupational asthma frequently manifest normal lung function at the time of presentation and it may be necessary to document functional impairment related to work exposure. Recognized patterns of derangement greater than 20% decline in PEFR over a work shift and a progressive decline in flow rates over the work week with improvement on weekends. Because of the potential

for delayed response, 24 hour records of PEFr using portable peak flow meters may be helpful.<sup>18</sup>

Appropriate drug use keeps most asthmatics out of emergency. Selection and stepwise use of drugs are, however, based on the severity of asthma. The mainstay of asthma therapy is the use of therapeutic agents such as aerosols or powders delivered directly into the lungs. This avoids the first pass metabolism in the liver. This method entails much lower doses having minimal side effects. Montelukast is the first Leukotriene receptor antagonist launched in the UK for the treatment of asthma. It is licensed for mild to moderate asthma, which is inadequately controlled by inhaled corticosteroids, and for exercise induced bronchoconstriction. Montelukast is the first of a new class of drugs for asthma. It is also licensed add-on therapy for adults and children over six years with mild to moderate persistent asthma inadequately controlled by inhaled corticosteroids. Montelukast is more effective than placebo at preventing Leukotriene-induced bronchoconstriction and produces a moderate but significant increase in the forced expiratory volume (FEV) at one second.

Montelukast was also reported to provide better control of exercise-induced bronchoconstriction. In one study, two of the 28 patients experienced transient abnormalities of liver function.<sup>1</sup> In one of the cases there was an increase in bilirubin and an increase in ALT.<sup>19</sup> Their findings were in agreement with the present study in which an increase in ALT was recorded in patients treated with montelukast. Treatment with both montelukast and inhaled beclomethasone result in improvement in multiple parameters of asthma control. No tachyphylaxis as effect of montelukast was recorded. However, the effect of beclomethasone on the mean FEV per second increased and equaled with the level of montelukast and then maintained an upward trend in the present study. It could be worthwhile to study the effects of beclomethasone for a period beyond 8 weeks.

Guidelines have been published on the step

wise management and treatment of asthma. The management includes regular monitoring of asthma using peak flow meters whereas the treatment plans vary according to mild, moderate and severe asthma. The treatment is given by using anti-inflammatory drugs in oral or inhaled form. The most effective treatment for acute asthma requires a systematic approach based on the aggressive use of sympathomimetic agents and objective monitoring of key indices of improvement. Multiple inhalations of a short-acting sympathomimetic, such as albuterol are the cornerstone of most regimens. Continuous nebulization of  $\beta_2$ -agonists has also been employed, but it is unclear if it is materially better than the other forms of treatment.<sup>20</sup>

Acute episodes of bronchial asthma are one of the most common respiratory emergencies and it is essential that the physician recognizes which episode of airway obstructions are life-threatening and which patients demand that level of care. These distinctions can be made readily by assessing selected clinical parameters in combinations with measures of expiratory flow and gas exchange. The presence of a paradoxical pulse, use of accessory muscles, and marked hyperinflation of the thorax signify severe airway obstruction, and failure of these signs to remit promptly after aggressive therapy mandates objective monitoring of the patients with measurements of arterial blood gases and PEFr. Patients with the most impairment typically require the most extensive therapy for resolution. If the PEFr is < 20% of predicted on presentation and does not double within an hour of receiving the preceding therapy the patient is likely to require extensive treatment, including glucocorticoids.

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