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Study of Role of Montelukast Added on Therapy to Inhaled Corticosteroids & □ Agonistsin Mild-Moderate Bronchial Asthma.

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Abstract
Bronchial asthma is a syndrome characterized by episodes of variable obstruction largely reversible either spontaneously or with treatment. There are various drugs like corticosteroids, Bronchodilators, Mast cell stabilizers & Leukotriene antagonists for preventing and treating bronchial asthma.
Aim: *This study was done to Assess the role of Montelukast, added on therapy to inhaled corticosteroids+β agonists(Standard therapy) in chronic mild to moderate bronchial asthma.*
Materials & Methods: *After getting approval from institutional ethical committee, 30 patients with history of bronchial asthma (in whom reversibility of airway obstruction was demonstrated with salbutamol inhalation) were selected for this study. Half of these patients received conventional treatment while other half received montelukast along with conventional treatment. All patients were recalled for follow up every week for 4 weeks and were assessed for improvement of symptoms with regard to peak expiratory flow rate(PEFR), Forced expiratory volume in 1 second(FEV1) & with subjective parameters like cough, Wheez, Dyspnoea & Sleeplessness.*
Results*: the frequency of using inhaler was reduced in 86% of patients in montelukast group. Peak expiratory flow & FEV1 were also significantly improved in montelukast group.*
Conclusion: *Montelukast added on therapy to inhaled corticosteroids & β agonists is very effective in treatment of mild to moderate bronchial asthma. It also helps in tapering the inhaler usage.*
Keywords: *Leukotriene An*tagonists, Montelukast, Peak expiratory flow rate(PEFR)

I. Introduction

Bronchial asthma is a syndrome characterized by episodes of variable obstruction, largely reversible either spontaneously or with treatment[1]. It is provoked either by external stimuli or internal stimuli. The external stimuli include dust, pollen, cold breeze, certain foodstuffs, smoke, certain drugs like β blockers, etc. Most of the times, when Asthma is provoked by external stimulus, it is considered as type 1 Hypersensitivity. The internal stimuli like exercise, emotions like fear, rage, etc. are also known to provoke asthma. On this basis asthma is classified as atopic (provoked by external stimuli) or non atopic (provoked by emotion, exercise, etc.). For management of any type of Asthma (atopic or Non Atopic), the standard therapy that is ordinarily used is a combination of inhaled corticosteroid & a β2-agonist for several years.[2] Though the prognosis with this treatment is fair, long term usage of these drugs result in a number of side effects like oral candidiasis, acne, sodium & water retention, muscle tremors, tachycardia, etc.. Moreover, there is also chance of decreased response to β2-agonists due to down regulation of β2- receptors on long term usage [3]. Hence long term use of these drugs should be averted

There are various drugs for treating asthma. These include corticosteroids, Bronchodilators, Mast cell stabilizers & Leukotriene antagonists. The pathogenesis of asthma and site of action of these drugs is illustrated below.

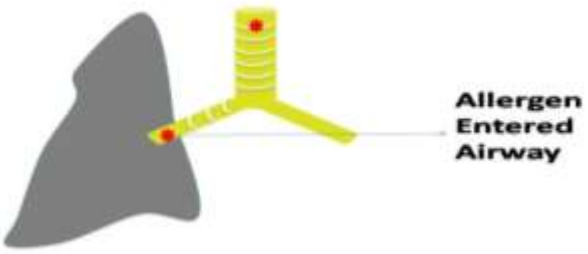


Figure 1 allergen has entered airway

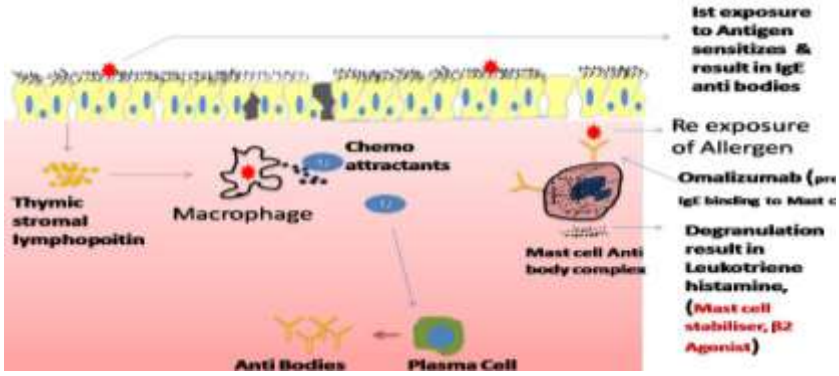


Figure 2 events occurring across respiratory epithelium

After the entry of allergen into the Airway, the structural cells in the airway express "Thymic stromal lymphopoitin", which regulates production of T-Helper cells 2[4]. The macrophages in the area attract T Helper cells 2 & esinophils by release of certain chemoattractants. T helper cells 2 boost production of IgE Antibodies from plasma cells. These Anti bodies bind to Mast cells and Basophils to form Mast cell/basophil-Antibody complex. On re exposure to allergen, the anti bodies tune mast cells to release chemical mediators like Leukotrienes, Histamine, etc. which are responsible for symptoms of Asthma.

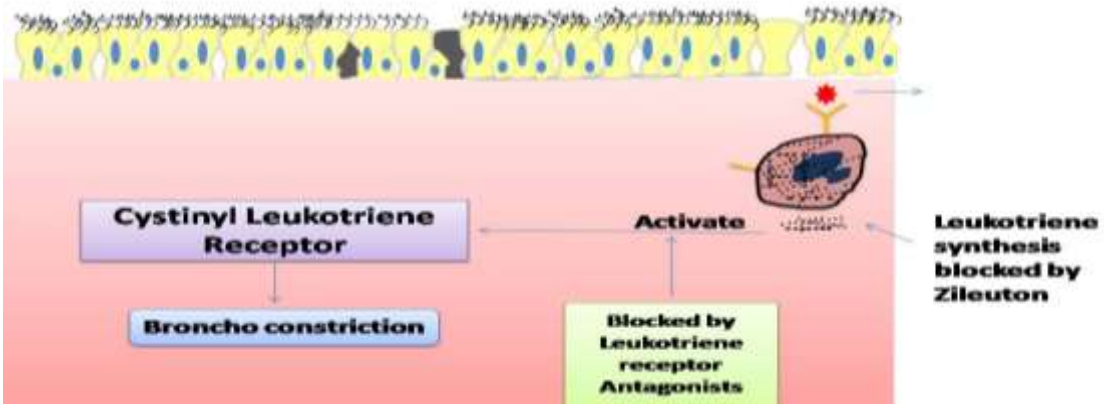


Figure 3 release of leukotrienes & bronchoconstriction

Leukotrienes are important mediators of Asthma & Bronchoconstriction occurs when they bind to cystinyl Leukotriene Receptors. This binding can be blocked by leukotriene Receptor Antagonists (Montelukast) .

Leukotriene synthesis Pathway

Arachodonic acid is formed by the damage of cell membrane either due to trauma or due to infections. Leukotrienes are derived from Arachidonic acid by lipoxygenase pathway as shown in the diagram.

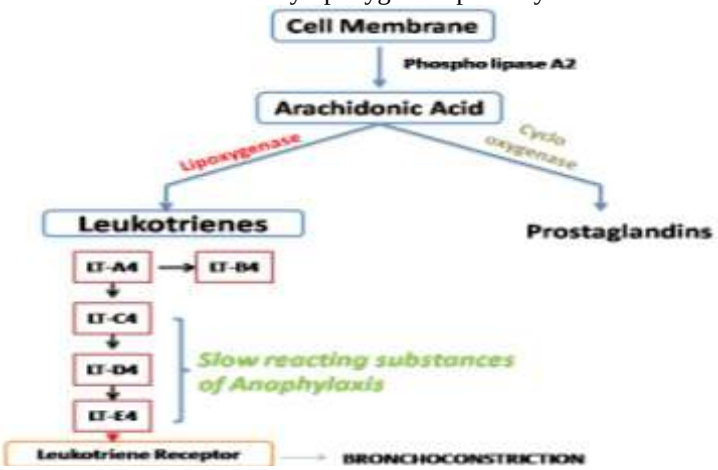


Figure 4 synthesis of leukotrienes

Leukotrienes are more potent inflammatory substances than prostaglandins[5]. There are four types of Leukotriens-LTB4, LTC4, LTD4 & LTE4 (LTA4 is considered as precursor). Of these LTC4, LTD4 & LTE4 are called slow reacting substances of anaphylaxis. All these play important role in many inflammatory reactions including Bronchial asthma. LTB4 is a potent chemotactic agent and attracts pro-inflammatory cells, e.g. neutrophils and eosinophils, into tissues.

The drug or drugs used as first line treatment for chronic mild persistent Bronchial asthma remained under intense scrutiny. According to expert panel guidelines [6], the ideal drug for chronic mild persistent Bronchial asthma should have following features—

1) Be easy to take
2) Improve symptoms of asthma
3) Improve pulmonary functions
4) Improve non specific Bronchial hyper reactivity
5) Decrease airway inflammation
6) Treat all corners with Asthma
7) Decrease exacerbation rates
8) Improve long term outcomes of disease
9) Have minimal side effects

Most of these can be assigned to leukotriene receptor Antagonists.

In this study our aim is to assess the role of Montelukast, a Lukotriene antagonist added on therapy to inhaled corticosteroids+β2 agonists(Standard therapy) in chronic mild to moderate bronchial asthma & Not those patients who do not respond to standard therapy.

II. Materials and Methods

After getting approval from institutional ethical committee, 30 Patients (aged between 20 – 50 years) were selected for this study from Government chest Hospital, Warangal, Andhra Pradesh. Lung Function tests (FEV1- Forced expiratory volume in 1 second) & peak expiratory flow rate were recorded in all patients prior to the start of study.

Study Period: January 2004 to February 2006. The study population (30 Patients) was selected according to the following criteria—

Inclusion criteria:

1) Only patients aged between 20-50 years (both male & female patients) were selected.
2) All patients had History of Bronchial asthma in which the reversibility of airway obstruction was demonstrated with salbutamol inhalation (≥12% increase of peak expiratory flow rate when measured using standard peak flow meter).
3) All patients were free from respiratory infections at least 4-8 weeks prior to case study.

Exclusion criteria:

1) Those patients who did not give consent for study
2) Pregnant women,
3) Patients with history of previous lung diseases like Pneumothorax & Haemoptysis etc.
4) Patients with Hepatic/Renal impairment
5) Alcoholic patients & Patients' with history of Drug Abuse

The study population comprising 30 patients did not have any of these exclusion criteria.

The study was explained to patients & their consent was taken. Patients were allocated in to two groups (15 in each group). One group was given Montelukast 10mg along with standard therapy i.e corticosteroid + β2 agoinist (Montelukast group) while the other group was treated with the routine standard therapy with a Placebo (Control Group). This is a double blind study. Patients & investigator are unaware of type of medication that was given to both groups.

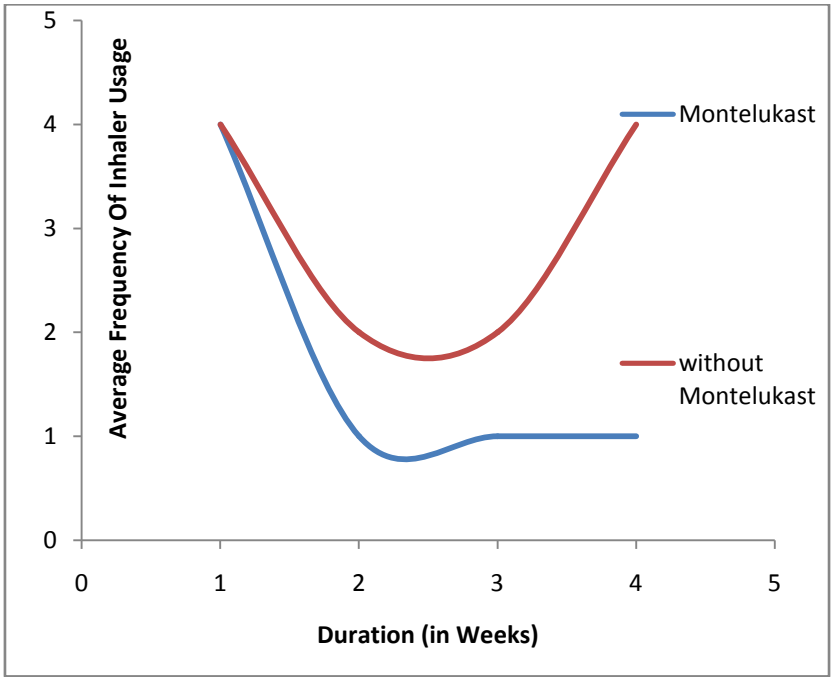
Two patients in the Montelukast group had exercise induced Asthma, 7 patients in montelukast group & 8 Patients in Control group had Dust & Pollen allergy, 3 patients in Montelukast group & 2 patients in control group had food allergy (brinjal, milk & milk products, non vegetarian diet).

All patients were called for follow up every week and were assessed for improvement of symptoms and their peak expiratory flow was recorded with a standard Peak Expiratory Flow Meter. The frequency of using Inhaler by the patient in that week was also noted. Subjective symptoms (cough, Wheeze, Dyspnoea, Sleeplessness) were graded every week by the Assistant. At the end of 4th week Lung Function tests were repeated.

Statistics : Descriptive statistics was used to analyze data. Results are indicated in percentages. graphs are used to illustrate results.

III. Results

The peak expiratory flow of patients on Montelukast was significantly better than the patients who were not on Montelukast. The incidence of using Inhaler was also decreased in 13 patients (86%) on montelukast. The peak expiratory flow these patients was improved despite the decreased use of β2 agonist & corticosteroid inhalers.



Subjective symptoms like cough, wheeze, dyspnoea, sleeplessness were decreased in montelukast group. These are illustrated in graph.

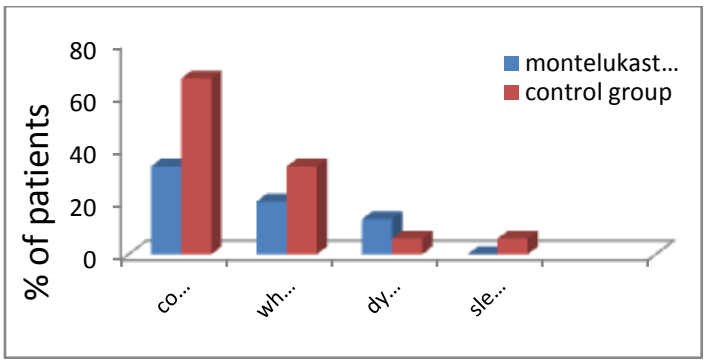


Figure 5 frequency of using inhaler

IV. Discussion

Bronchial asthma is reversible obstructive airway disease and troubles the patients with shortness of breath. Previously, when there were no inhalers, if there was an asthma attack suddenly, Patient had to run to a hospital for getting treatment. In the hospital, such patients were treated by giving Deriphylline injection immediately while keeping the patient in slant position with back rest & by providing oxygen supplementation. If it was not controlled, I.V. aminophylline drip + nebulisation were used. The main drawback of this treatment was that patient had to run to hospital whenever he gets an attack.

With time, the Corticosteroid inhalers and salbutamol/salmetrol inhalers evolved which can be used by patient without depending on others. Patients are generally advised to carry these inhalers with them. Whenever the patient doubts, he has to take 2 puffs (100 metered dose/puff) to prevent sudden attack. In winter, patient has to inhale same dose twice a day (morning & night) & also whenever necessary.

But long term use of corticosteroid inhalers results in fungal infections of throat, tongue and also result in hoarseness of voice. Similarly prolonged β agonist use is also not advised, especially in older age groups. β adrenoceptor agonists have inotropic and chronotropic effects that can increase arrhythmias and cardiomyopathy. They can also worsen or induce myocardial ischaemia and cause electrolyte disturbances that contribute to arrhythmias. Tremor is a well known distressing adverse effect of β-agonist administration.

In this study, it was seen that Montelukast helped in tapering of these drugs. The frequency of using inhaler was decreased from 4 times a week to 1 time a week in 86% of patients on Montelukast. It was also seen that there was a significant improvement in peak expiratory flow of all patients on montelukast. In a similar study [7], done on patients with aspirin intolerant asthma, there was significant improvement in Peak expiratory flow & Forced expiratory volume in 1 second (FEV1). On contrary, in a study[8] involving patients who do not respond to standard therapy it was seen that the peak expiratory flow of only few patients was improved significantly with Montelukast added on therapy.

In this study, it was seen that 2 patients with exercise induced Asthma were not much benefitted with Montelukast. However in another study[9], it was seen that Montelukast was as effective as beta agonists for treatment of exercise induced asthma. So beta agonist may be replaced with Montelukast monotherapy in these cases.

There are few adverse effects associated with montelukast In our study, Patients were asked to report any adverse effects they might experience during the treatment period. 3 patients(20%) reported anorexia and abdominal fullness. One patient (6%) complained mild abdominal pain & constipation from 5th day onwards. 26% of patients(4 patients) complained of mild headache during evening times at the end of 1st week.

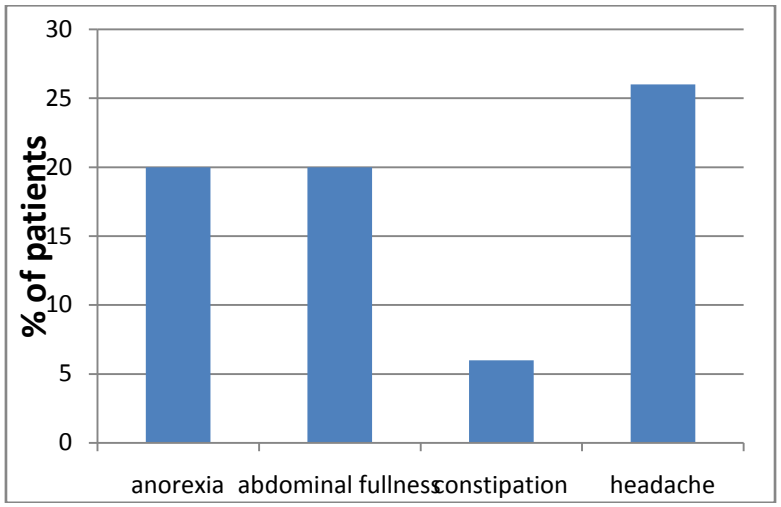


Figure 6 Adverse Effects of Montelukast

There are also few reports[10,11] of Churg-Strauss syndrome. According to a retrospective study[12] from 2008 – 2013, significant number of pediatric patients experienced side effects like over activity & abdominal pain. However in another study[13] involving large number of pediatric patients, the frequency of adverse effects was insignificant. Also a study[14] conducted on pregnant women claimed that leukotriene antagonists are not associated with major teratogenic effects. However leukotriene antagonists must be used with caution in pregnant women.

V. Conclusion

Montelukast added on therapy to inhaled corticosteroids & β agonists is very effective in treatment of mild to moderate bronchial asthma. It also helps in tapering the inhaler usage.

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