ROLE OF LEUKOTRIENE RECEPTOR ANTAGONIST IN ACUTE SEVERE ATTACK OF BRONCHIAL ASTHMA IN COMPARISON WITH CONVENTIONAL THERAPY

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ABSTRACT:
This study was designed to determine the role of leukotriene receptor antagonist in acute severe attack of bronchial asthma in comparison with conventional therapy. Asthma is a chronic inflammatory lung disease in both the developed and developing countries. Asthmatic patients are at risk of worsening of disease characterized by an increased breathlessness, cough, chest discomfort and wheezing and decreased in expiratory airflow rate. Leukotrienes are lipid mediators synthesized from arachidonic acid, an element of the phospholipid bi-layer membranes. leukotriene D₄ (LTD₄), and leukotriene E₄ (LTE₄), which are potent chemo attractants. These chemical mediators are involved in the pathogenesis of asthma. Study results reveled the effectiveness of leukotriene receptor antagonist in preventing many types of aggravated asthmatic responses. Oral administration of leukotriene receptor antagonist in acute asthmatic patients improves airway function. Once-daily treatment with 10 mg of montelukast, as compared with conventional therapy, provided significant protection against severe broncho-constriction. Study also shows that there was no worsening of the disease. Parameters strongly confirmed the role of leukotriene receptor antagonist when in addition added with steroid therapy in the treatment of acute asthma, there were a smooth improvement was noticed.

Keywords: Leukotriene receptor antagonist, acute asthma, conventional therapy.

INTRODUCTION
Asthma is the most prevalent chronic disease of childhood, affecting >4 million children in the United States (Mannino et al., 2002). The number of patients diagnosed with asthma is increasing worldwide (Woolcock, 1997), particularly among children and adolescents (Sly, 1999). Chronic inflammation of the airways is a major component of the pathophysiologic mechanism of asthma. Cysteinyl leukotrienes play a key role in mediating this pathologic process (Drazen et al., 1999). Antileukotriene agents such as montelukast act by blocking the effects of the cysteinyl leukotrienes and have proved very effective in controlling symptoms of asthma among adults and in reducing markers of chronic inflammation among adults (Reiss et al., 1998) and children (Knorr et al., 2001).

Current clinical practice guidelines from the National Heart, Lung, and Blood Institute (NIH, 1997) and the Global Initiative for Asthma (GINA) (NIH, 1998) recommend the use of anti-inflammatory controller therapy for the long-term treatment of persistent asthma. Inhaled corticosteroids (ICS) are recommen-

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ded and are used widely as first-line controller agents (NIH, 1997, NIH, 1998), with leukotriene-modifying agents being recommended as alternative or add-on therapies. Studies have reported variable results when comparing montelukast with ICS in improving lung function end points such as peak flow and forced expiratory volume in 1 second (FEV₁) (Kanniess et al., 2002). To obtain a more complete profile of therapeutic efficacy, measures of asthma control should also address the use of rescue medications and asthma-related health care utilization. Evaluating asthma control with these end points has shown sensitivity and responsiveness in studies among mild asthmatic patients, correlating with patient symptoms (Santanello et al., 1999). Leukotriene receptor antagonists (LTRAs) have been suggested both as suitable monotherapy and add-on therapy to ICS for the treatment of asthma (Laviolette et al., 1999).

The cysteinyl leukotrienes (LTC₄/D₄/E₄) induce bronchoconstriction, mucus hypersecretion, mucosal edema, enhance airway hyperreactivity, and act as chemoattractants for eosinophils in the airway (Gauvreau et al., 2001). Therefore, it is not surprising that LTRAs improve lung function, attenuate bronchial hyper-responsiveness, and reduce the number of exacerbations in patients with mild to moderate asthma (Barnes, 2000). Moreover, addition of LTRAs to ICS results in better control of asthma (Cristian-Virchow et al., 2000) and can decrease the requirement for ICS (Loe Dahl et al., 1999). Effects of LTRAs on inflammatory markers are less certain. Treatment with LTRA montelukast has resulted in a significant decrease in serum eosinophil cationic protein and both sputum (Yoshida et al., 2000) and peripheral blood eosinophils (Pizzichini et al., 1999). Oral leukotriene receptor antagonists increase the control over the disease in both children and adults and can reduce the severity of the asthma. Acute asthma is a common medical emergency that is often poorly managed despite well defined recommendations for its assessment and treatment. However, the role of the leukotriene receptor antagonists in the treatment of acute severe attack of asthma is still unknown. The question now is exactly how effective is the leukotriene antagonist (Montelukast), when compared with the other conventional therapy in the treatment of the acute asthma. The current study examines the effect of oral leukotriene receptor antagonist in the treatment of acute severe attack of asthma in comparison with the other conventional therapy.

**METHODOLOGY**

This Descriptive comparative prospective study was conducted during 2008-2009, at Department of Chest Medicine, Liaquat National Post Graduate Medical Center (LNPMC), Karachi and Department of Pharmacology, Faculty of Pharmacy, University of Karachi. In this study, 100 adult asthmatic patients were randomized into two groups.

**Experimental details**

Group A was considered as control and conventional therapy was mentioned with oxygen, β-agonists (salbutamol 5 mg nebulizer), corticosteroids and methylzanthine. In group B along with standard conventional therapy montelukast 10 mg was added on daily basis. The classification of asthma was based on clinical history and examination and pulmonary function parameters, according to international guidelines. After taking the consent, patients go through the spirometry according with the reproducibility and acceptability criteria of the American Thoracic Society, followed by a mandatory salbutamol nebulization. Patients who met the eligibility criteria were allocated in the study.

**Pulmonary Function Tests**

Pulmonary function was measured by spirometry using a calibrated computerized pneumotachograph spirometer (Jaeger Masterscope PC, Hoechberg, Germany). Forced vital capacity (FVC), FEV₁, FEV₁/FVC ratio, forced expiratory flow
through the mid portion of the vital capacity (FEF25–75) and peak expiratory flow (PEF) were determined before and after the treatment challenge. The procedure for all pulmonary function tests was (a) three normal tidal volume breaths, (b) maximal inhalation, (c) forced maximal exhalation, and (d) maximal inhalation. Resting baseline pulmonary function was established before each challenge by selecting the best of three resting pulmonary function tests based on the highest sum of FVC and FEV1. Although there are a number of systems to choose from, the following is the method recommended by the Global Initiative for Obstructive Lung Disease (Global Initiative for Chronic Obstructive Lung Disease, 2007) (Table 1).

DATA ANALYSIS

Data will be analyzed using the SPSS version 10.0 Pearson’s Chi- square test and Z – test of proportion will be used for comparison of qualitative output response. Student t – test will be used for comparison of numeric output response. Shapiro-Wilk test statistics will be used to test for normality. Levene’s test will be used to test for homogeneity of variances. Statistical significance will be taken at p< 0.05.

RESULTS

The results revealed that there was statistically significant difference between the groups treated with conventional therapy alone to those treated with conventional therapy and leukotriene inhibitors.

Study was conducted on 100 patients of acute asthma. Fifty patients were included in each group in this study based on inclusion and exclusion criteria. The mean age of the patients in group A was 48.3 ± 7.49 while in group B mean age was 51.34 ± 8.72. (p = 0.42) Majority of the patients (36%) were enrolled between the ages of 50 to 60 years. Gender wise distribution of patients in group A shows (58%) male and 42% females while in group B (68%) male and (16%) female were enrolled (p = 0.29).

Our study results shows that duration of asthma (years) in group A was 10.57% (± 5.37) while in group B 12.42% (± 5.21) was noticed (p = 0.62). (Table 2)

All the parameters of the study were recorded at the time of admission as a base line then after 24 hours, 48 hours, 72 hours, 01st week, 02nd week and 4th week respectively.

<table>
<thead>
<tr>
<th>Table-1</th>
<th>GOLD Spirometric Criteria for COPD Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Mild COPD</td>
<td>* FEV1/FVC &lt; 0.7  * FEV1 &gt;/= 80% predicted</td>
</tr>
<tr>
<td>II. Moderate COPD</td>
<td>* FEV1/FVC &lt; 0.7  * 50% &lt;/= FEV1 &lt; 80% predicted</td>
</tr>
<tr>
<td>III. Severe COPD</td>
<td>* FEV1/FVC &lt; 0.7  * 30% &lt;/= FEV1 &lt; 50% predicted</td>
</tr>
<tr>
<td>IV. Very Severe COPD</td>
<td>* FEV1/&lt; 0.7  * FEV1 &lt; 30% predicted or FEV1 &lt; 50% predicted with chronic respiratory failure</td>
</tr>
</tbody>
</table>
Analysis of respiratory rate (breath/minute) were also recorded in both groups on the given time periods. Respiratory rate was found to be improved in both groups of acute asthma with significant $p$ value (0.05). (Table 3)

Comparison of pulse rate (beats/minute) was also observed. At the time of base line measurements, tachycardia was found and base line heart rate was (118.47 ± 4.56 beats/minute) in group A and (115.22 ± 5.62 beats/minute) in group B. In the first 24 hours little bit improvement was observed in heart rate as compare to base line measurement but between the groups there was no significant change was noticed. The $p$ value was observed ($p = 0.08$). (Table 3) Oxygen saturation (%) of patients in group A was (88.45 ± 4.74 %) and in group B (89.88 ± 4.31%) ($p=0.53$) at the time of enrollment. In our study, it was found that when patients admitted with acute asthma their oxygen saturation was found < 90% (Table 3). After treatment, in the first 24 hours

### Table 2
History Of Duration of Asthma (Years)

<table>
<thead>
<tr>
<th>Duration of asthma (years)</th>
<th>Group A (n = 50) (Mean ± SD)</th>
<th>Group B (n = 50) (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.57 ± 5.37</td>
<td>12.42 ± 5.21</td>
<td>0.62*</td>
</tr>
</tbody>
</table>

Group A = On conventional therapy  
Group B = On conventional therapy + leukotriene receptor antagonist (Montelukast)  
* = significant, ** = Moderately significant, *** = Highly significant

### Table 3
Changes in respiratory rate, pulse rate and oxygen saturation over time

<table>
<thead>
<tr>
<th>Time period</th>
<th>Respiratory rate (breath/minute)</th>
<th>Pulse rate (beats/minute)</th>
<th>Oxygen saturation(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (Mean ± SD)</td>
<td>Group B (Mean ± SD)</td>
<td>$p$ = value</td>
</tr>
<tr>
<td>Base line</td>
<td>30.71 ± 4.12</td>
<td>31.23 ± 2.21</td>
<td>0.58</td>
</tr>
<tr>
<td>After 24 hours</td>
<td>24.26 ± 3.41</td>
<td>25.13 ± 3.19</td>
<td>0.05</td>
</tr>
<tr>
<td>After 48 hours</td>
<td>22.73 ± 2.10</td>
<td>21.71 ± 2.55</td>
<td>0.05</td>
</tr>
<tr>
<td>After 72 hours</td>
<td>20.55 ± 1.45</td>
<td>19.45 ± 2.14</td>
<td>0.001**</td>
</tr>
<tr>
<td>After 01 weeks</td>
<td>19.81 ±1.02</td>
<td>17.26 ± 1.34</td>
<td>0.001**</td>
</tr>
<tr>
<td>After 02 weeks</td>
<td>18.60 ±1.01</td>
<td>15.51 ± 1.12</td>
<td>0.001**</td>
</tr>
<tr>
<td>After 04 weeks</td>
<td>17.94 ±1.67</td>
<td>14.11 ± 1.04</td>
<td>&lt;0.0001 ***</td>
</tr>
</tbody>
</table>

Group A = On conventional therapy,  
Group B = On conventional therapy + leukotriene receptor antagonist (Montelukast)  
* = significant, ** = Moderately significant, *** = Highly significant
in both groups there were improvement in oxygen saturation in both groups but between the groups there were no significant change was noticed ($p = 0.06$).

Base line peak expiratory flow rate (PEFR) L/Minute) shows $p$ value ($p = 0.47$). But after 24 hours, significant change was noticed in both groups (Table 4), $p$ value was significant ($p = 0.05$). In group B, PEFR was significantly improved with passage of time.

### Table 4
Comparison of Peak Expiratory Flow Rate (L/Minute)

<table>
<thead>
<tr>
<th>Time period</th>
<th>Group A (L / Minute)</th>
<th>Group B (L / Minute)</th>
<th>P = Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Mean ± SEM)</td>
<td>(Mean ± SEM)</td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>175.21 ± 25.36</td>
<td>178.87 ± 27.62</td>
<td>0.47</td>
</tr>
<tr>
<td>After 24 hours</td>
<td>185.34 ± 25.34</td>
<td>188.01 ± 31.52</td>
<td>0.05*</td>
</tr>
<tr>
<td>After 48 hours</td>
<td>190.62 ± 26.74</td>
<td>194.46 ± 33.47</td>
<td>0.05*</td>
</tr>
<tr>
<td>After 72 hours</td>
<td>198.41 ± 28.74</td>
<td>201.51 ± 37.67</td>
<td>0.04*</td>
</tr>
<tr>
<td>After 01 week</td>
<td>203.29 ± 28.30</td>
<td>224.74 ± 39.81</td>
<td>0.001***</td>
</tr>
<tr>
<td>After 02 week</td>
<td>209.61 ± 29.48</td>
<td>232.12 ± 41.49</td>
<td>0.001**</td>
</tr>
<tr>
<td>After 04 week</td>
<td>217.76 ± 20.33</td>
<td>238.64 ± 41.41</td>
<td>&lt; 0.0001***</td>
</tr>
</tbody>
</table>

Group A = On conventional therapy
Group B = On conventional therapy + leukotriene receptor antagonist (Montelukast)

### Table 5
Changes in spirometric parameters over time

<table>
<thead>
<tr>
<th>Time period</th>
<th>Forced Expiratory Volume (FEV1)</th>
<th>Forced Expiratory Volume% (FEV1 % PRED)</th>
<th>Forced Expiratory Volume / Forced Vital Capacity (FEV1/FVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (Mean ± SD)</td>
<td>Group B (Mean ± SD)</td>
<td>Group A (Mean ± SD)</td>
</tr>
<tr>
<td></td>
<td>$p$ = value</td>
<td></td>
<td>$p$ = value</td>
</tr>
<tr>
<td>Base line</td>
<td>1.59 ± 0.25</td>
<td>1.62 ± 0.34</td>
<td>0.63</td>
</tr>
<tr>
<td>After 24 hours</td>
<td>1.84 ± 0.21</td>
<td>1.95 ± 0.26</td>
<td>0.05*</td>
</tr>
<tr>
<td>After 48 hours</td>
<td>2.14 ± 0.11</td>
<td>2.13 ± 0.35</td>
<td>0.06</td>
</tr>
<tr>
<td>After 72 hours</td>
<td>2.28 ± 0.24</td>
<td>2.59 ± 0.55</td>
<td>0.04*</td>
</tr>
<tr>
<td>After 01 weeks</td>
<td>2.66 ± 0.34</td>
<td>2.89 ± 0.41</td>
<td>0.001**</td>
</tr>
<tr>
<td>After 02 weeks</td>
<td>2.81 ± 0.18</td>
<td>3.05 ± 0.13</td>
<td>0.0001**</td>
</tr>
<tr>
<td>After 04 weeks</td>
<td>2.94 ± 0.17</td>
<td>3.29 ± 0.16</td>
<td>0.0001**</td>
</tr>
</tbody>
</table>

Group A = On conventional therapy
Group B = On conventional therapy + leukotriene receptor antagonist (Montelukast)

* = significant,** = Moderately significant, *** = Highly significant
In comparison of force expiratory volume % (FEV1 PRED) between the group A and group B, after 24 hours significant change was noticed in group B. The results were significant after 24 hour of the treatment. The results of forced expiratory volume/forced vital capacity (FEV1/FVC %) shows a significant difference after 24 hours of the treatment with conventional therapy in group A and conventional therapy plus leukotriene receptor antagonist (Montelukast) from the baseline measurement (Table4). Similarly, FEV1% PRED was highly significant in group B patients of acute asthma after 04 week of therapy. Comparison of forced expiratory volume/forced vital capacity (FEV1/FVC) showed clinically important results. In group B patients of acute asthma, after 24 hours the result was significantly observed, But, after 48 hours, there was no significant difference noticed in both groups. After 72 hours, again an improvement was notice in group B patients of acute asthma with a significant p value (Table 5).

DISCUSSION

Although > 35 clinical trials with this drug class reveal efficacy in asthma management, the issue of the positioning of the anti-leukotrienes in asthma management guidelines continues to attract much attention: in particular, whether they should be used in step 2 of the asthma management guidelines (either as an alternative or in addition to low-dose inhaled corticosteroids), or whether they sit more comfortably at step 3 as an alternative to increasing the dose of inhaled steroid or the introduction of a long-acting β2-agonist. Clinical trials (Drazen et al., 1999) show efficacy across the whole spectrum (mild, moderate, and severe).

An interesting feature of most clinical studies is that some patients appear to show better responses than others (Ind, 1999), suggesting that leukotrienes may play a more important role in some patients. This highlights the importance of individualizing treatment to suit the patient, and ensuring that management guidelines are flexible to allow this. Recent studies (Ind, 1999, Malmstrom et al., 1999) that have directly compared the clinical efficacy of anti-leukotrienes with inhaled corticosteroids suggest that they are unlikely to replace these drugs in asthma management, but provide no reason to believe that the addition of a leukotriene modifier to a multifaceted asthma treatment program will not have a complementary effect. In patients with moderate-to-severe chronic persistent asthma, leukotriene-modifier therapy can be combined with inhaled glucocorticoids to maintain control of asthma with lower doses of the latter, or it can be added to an existing regimen to achieve better control of asthma (Drazen et al., 1999).

In our study, oral montelukast was compared with conventional therapy associated with a rapid benefit as evidenced by a significant improvement in FEV1. The benefit attributed to montelukast was not confounded by an increased use of β-agonists or corticosteroids and was accompanied by trends toward improvements in clinical outcomes such as treatment failures. Oral montelukast demonstrated a tolerability profile comparable to conventional therapy, and no unexpected adverse experiences were noted.

Several studies have examined new interventions in acute asthma that could provide rapid and sustained relief from airflow obstruction, in addition to current standard treatment. For example, inhaled ipratropium may provide a modest bronchodilator benefit and an improvement in hospital admission rates, particularly in patients with severe asthma exacerbations (Rodrigo, 2002), and ipratropium is now used frequently for asthma in the acute setting (Stoodley et al., 1999). Others have suggested, however, that there is little if any added benefit of ipratropium above that of standard therapy with β-agonists (Silverman, 2000). Moreover, anti cholinergics do not appear to be effective for patients whose initial response to β-agonists is impaired (McFadden et al., 1997), and at this point, there is no clear consensus regarding
their use (Silverman, 2000). Other interventions for acute asthma that are current areas of active research include intravenous magnesium (Rowe et al., 2001), xanthines (Parameswaran et al., 2001), and inhaled helium/oxygen mixtures (Rodrigo et al., 2001).

In our study, such type of currently available remedies were used as conventional therapy but when leukotriene receptor antagonist was added along with this conventional therapy, it has been observed that the cumulative effect of the medications in the group which was treated by the conventional therapy along with leukotriene receptor antagonist (Montelukast) was prominent.

As we know that leukotriene pathways are activated in acute asthma, as evidenced by elevations in urinary leukotriene excretion reported elsewhere (Sampson et al., 1995). Leukotrienes are produced during asthmatic reactions by cells involved in the pathogenesis of asthma. However, the most convincing evidence of a causative role of leukotrienes in asthma comes from studies of the effectiveness against asthma of drugs that inhibit the action or formation of leukotrienes. Studies suggesting that these drugs may improve rhinitis (Donnelly et al., 1995), although such an effect may be an added benefit for patients with asthma. In our study, results reveled the effectiveness of leukotriene receptor antagonist in acute asthma.

Our study results and all the parameters that were observed strongly confirmed the role of leukotriene receptor antagonist when in addition added with steroid therapy in the treatment of acute asthma, there were a smooth improvement was noticed. This study also confirmed previous observations from previous trials, that leukotriene receptor antagonists provide additional clinical benefit to patients using constant doses of inhaled corticosteroids but with incomplete asthma control (Altman et al., 1998). Such additive clinical benefit of leukotriene receptor antagonists and inhaled corticosteroids has also been demonstrated in stable patients on high-dose inhaled corticosteroid therapy (Lofdahl et al., 1999, Tamaoki et al., 1997). One of these trials (Lofdahl et al., 1999) showed that inhaled corticosteroids can be tapered when a leukotriene receptor antagonist was given concomitantly. Oral leukotriene receptor antagonists may play a role in this challenging patient population. Future head-to-head studies will need to compare the relative merits of the different agents used concomitantly to achieve better asthma control.

**CONCLUSION**

The data reviewed here are inadequate to support a recommendation that patients with moderate-to-severe persistent asthma should be treated with leukotriene-modifier drugs alone, but they provide reason to believe that the addition of a leukotriene modifier to a multifaceted asthma-treatment program will have a salutary effect. In patients with moderate-to-severe chronic persistent asthma, leukotriene-modifier therapy can be combined with inhaled glucocorticoids to maintain control of asthma with lower doses of inhaled glucocorticoids, or it can be added to an existing regimen to achieve better control of asthma.

Finally, because the leukotriene modifiers are the first treatment for asthma to result from a search for an inhibitor of a specific biologic process, these new drugs should teach us much about the patho-physiology of asthma while providing orally available, safe, and effective therapy. In the future, there may be scope for novel therapies that modify the pathogenesis and/or disease course both in asthma and COPD.

**REFERENCES**


