Short-term effects of montelukast in stable patients with moderate to severe COPD

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Summary This study aims to investigate the possibility of additional value of leukotriene receptor antagonist (LTA) on dyspnea score, arterial blood gases (ABG), pulmonary function tests (PFTs), and quality of life (St. George QoL) in chronic obstructive pulmonary disease (COPD) patients. In this randomized, prospective, single-blind, and controlled study, 117 non-reversible COPD patients defined by global initiative for chronic obstructive lung disease (GOLD) criteria were randomized to receive ipratropium bromide, formoterol and montelukast (n:58, montelukast group) or ipratropium bromide and formoterol (n:59, control group) after a 2-week run-in period. There was no significant demographic difference between the two groups (P > 0.05). Baseline ABG, PFT, visual analogue scores (VAS), and QoL scores were obtained and at first month and second month, PFT, VAS, and QoL scores were repeated and ABG was obtained at second month and the values were compared with baseline values. As the result of the comparison, there was significant increase in vital capacity, FVC, FEV\textsubscript{1}, VAS, and PaO\textsubscript{2} parameters (P < 0.05), and a significant decrease in the QoL scores (P < 0.05) in the montelukast group. These parameters did not show any difference in the control group (P > 0.05). Sputum samples that could be obtained in 24 of the COPD patients were evaluated and in the montelukast group, there was a decrease in neutrophilic activity after treatment (n:13) (P:0.059). These results suggest that LTA that is used additionally in routine treatment protocol can produce additive improvement on PFT, dyspnea score and especially QoL in patients with stable COPD and for these reasons, LTA may be taken into account when there is need for an additional anti-inflammatory treatment in COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive development of airflow limitation that is not fully reversible. COPD has been increasingly recognized as an inflammatory disease characterized by sputum neutrophilia and, in some cases, eosinophilia. Patients with COPD classically have neutrophilic bronchial inflammation and increased airway concentration of the neutrophil chemoattractant leukotrienes. Neutrophil recruitment to the airway is thought to be an important component of the ongoing inflammation and progression of chronic obstructive pulmonary disease. Increased numbers of neutrophils are found in bronchial lavage samples and bronchial biopsy specimens from subjects with COPD even when they are clinically stable. There is evidence that the decline in forced expiratory volume in the first second (FEV₁) is related with airway neutrophilia. Therefore, the fact that neutrophil enzymes can cause all the pathological features of COPD, it has long been thought that neutrophils play a central role in the pathogenesis and progression of COPD.

Leukotriene B₄ (LTB₄) and interleukine 8 (IL-8) are both potent chemoattractants capable of promoting neutrophil transendothelial migration, and increased levels of these two chemoattractants have been found in secretions from patients with COPD, particularly those with severe stages. LTB₄ is a proinflammatory derivative of arachidonic acid. It upregulates the neutrophil adhesion molecule, and is both a potent neutrophil chemoattractant and a neutrophil activator. Cysteinyl leukotrienes (LTC₄, LTD₄ ve LTE₄) are known to induce mucus secretion, inflammatory cell infiltration, increase vascular permeability and tissue edema, damage ciliary ciliens, and cause severe bronchoconstriction. In spite of many studies with LTAs in asthma, there have been very few studies about their anti-inflammatory use in COPD.

We have performed a randomized, prospective, single-blind, controlled trial to assess the effects of leukotriene receptor antagonist (LTA), montelukast, on health-related quality of life (QoL), pulmonary function test (PFT), dyspnea score, arterial blood gas (ABG), and sputum neutrophil content.

Methods

One hundred and seventeen stable COPD patients defined by the global initiative for chronic obstructive lung disease (GOLD) criteria were recruited in our outpatient respiratory department between December 2002 and July 2003. Inclusion criteria at entry were chronic airflow impairment (percentage of FEV₁ < 80% and FEV₁/FVC < 70%), clinically stable condition with no exacerbation for 6 weeks prior to assessment, non-reversible airway obstruction, non-atopic patients and clinically stable co-morbidity. The patients who had a change less than 12% or absolute 200 ml in FEV₁ after 400 μg salbutamol inhalation were accepted as having non-reversible airway obstruction. Patients were randomized to receive ipratropium bromide (4 × 40 μg), formoterol (2 × 12 μg) and montelukast (10 mg every night) (n=58) or ipratropium bromide and formoterol (n:59) following the 2-week run-in period. During run-in period, all patients were prescribed to use the same drugs, ipratropium bromide and formoterol to standardize the treatment. Salbutamol inhaler was used as rescue medication. The first patient who had the inclusion criteria had been randomized by throwing a coin and the following patients had treatment consecutively.

Age, smoking status, exacerbations in the last year, duration of COPD, co-morbidity, and physical examination findings were noted. After run-in period, baseline ABG, PFT, visual analogue scores (VAS), health-related QoL called St. George’s Respiratory Questionnaire (SGRQ) which include symptom score, activity score, impact score and total score, and sputum samples were obtained. At the first and the second month of the study, PFTs, VAS, and health-related QoL scores were measured. ABG and sputum samples were obtained at the second month.

Pulmonary function tests

PFT were done with Jaeger Master Screen Pneumo Device (Jaeger Co, Hoechberg, Germany) by the same technician every time. Spirometric parameters, FEV₁, forced vital capacity (FVC), vital capacity (VC), FEV₁/FVC, and peak expiratory flow (PEF) were measured.

Dyspnea score assessment

VAS was used for assessment of dyspnea level. Patients were asked for marking the line that is 100 mm according to feeling of dyspnea. 100 mm was defined as dyspnea always present.

Quality of life measurement

QoL was assessed using Turkish translation of SGRQ, 50-item disease-specific questionnaire that
provides an overall measure for QoL with subscale scores in three areas: symptom, activity, and impact of disease on daily life. To calculate, the total and subscale scores, each item has a unique empirically derived ‘weight’ from zero to 100 with a score of 100 indicating maximum disability.7

Arterial blood gas

ABG analysis of the cases was performed by Roche OMNI C BG/ISE device.

Sputum processing and analysis

Four slides were prepared from the sputum samples, where two of them stained with hematoxylin-eosin, and the other two with giemsa. The criteria for the adequacy of the material were the presence of alveolar macrophages or respiratory epithelial cells. Single-blind pathologic evaluation was performed under light microscopy. The density of inflammation was divided into four categories (+1, +2, +3, +4) subjectively. Then, 10 high power fields where the inflammatory cells are most dense were evaluated to determine the percentages of neutrophils and eosinophils.

Subjects gave informed consent agreement for their participation in this trial. The study protocol was approved by the Hospital Ethics Committee.

Statistical analysis

The SPSS program (SPSS, 10.0 Inc, Chicago, IL, USA) was used to analyze the data. The arithmetic mean and standard deviation were calculated for all variables. For the analysis of COPD severity with other parameters (gender, occupation, smoking status, treatment modality, exacerbations in a last year, comorbidity, and physical examination findings), χ²-test was used. Comparison of the montelukast group and control group according to PFT, VAS and SGRQ scores was done by t-test. Comparison of percent changes in montelukast group and control group was done by Student’s t-test. Fisher’s exact test was used for the comparison of neutrophilic content of sputum between two groups. P<0.05 was accepted as an statistically meaningful.

Results

One hundred and seventeen patients (100 male, 17 female) with median age 65.72±9.11 (44–84) participated in the study. There was no significant difference between the two groups about age, smoking status, duration of disease, ABG, PFT, VAS, and SGRQ scores (symptom, impact, activity, and total) at the beginning of the study (P>0.05)(Table 1).

At the end of the second month, a significant improvement had been obtained in the pulmonary function parameters (FEV₁, FVC, FEV₁/FVC, PEF) of the montelukast group (P<0.05) (Fig. 1). FEV₁, FVC(%), FEV₁/FVC and PEF values were increased to 1.54±0.48 l (95% confidence interval (CI) 1.48–1.72), 73.9±12.6 (95% CI 69.88–76.50), 61.3±6.8 (95% CI 59.47–63.07), 45.8±18.4 (95% CI 40.96–50.65), respectively. There was not any significant change in the parameters above of the other group (P>0.05).

The QoL and VAS scores also significantly improved in the montelukast group at the end of second month (P<0.05) (Figs. 2 and 3). The basal symptom, impact, activity and total QoL scores of the montelukast group were 49±12.8 (95% CI

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and physiological findings of two groups.</th>
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<tbody>
<tr>
<td></td>
<td>LTA (+) (n:58)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>52/6</td>
</tr>
<tr>
<td>Age (year)</td>
<td>64.5±0.8</td>
</tr>
<tr>
<td>Duration of disease (year)</td>
<td>8.4±5.7</td>
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<tr>
<td>Exacerbation number (per year)</td>
<td>0.7±0.9</td>
</tr>
<tr>
<td>Smoking history (pack year)</td>
<td>51.5±31.7</td>
</tr>
<tr>
<td>Co-morbidity (–) (%)</td>
<td>34.5</td>
</tr>
<tr>
<td>FVC (lt)</td>
<td>2.5±0.8</td>
</tr>
<tr>
<td>FEV₁ (lt)</td>
<td>1.4±0.5</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>55.0±11.3</td>
</tr>
<tr>
<td>PEF (%)</td>
<td>41.5±18.7</td>
</tr>
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</table>

*χ²-test.
**Student’s t-test.
45.63–52.35), 35.5 ± 17.9 (95% CI 30.75–40.16),
54.9 ± 18.5 (95% CI 50.03–59.78), and 43.3 ± 16.1
(95% CI 39.04–47.50) and at the end of the second
month they were all improved to 42.8 ± 13.0 (95%
CI 39.41–46.25), 23.7 ± 13.4 (95% CI 20.10–27.16),
38.4 ± 13.6 (95% CI 34.83–41.99), and 30.9 ± 12.6
(95% CI 27.62–34.24), respectively. Basal VAS scores
65.2 ± 10.0 mm (95% CI 59.68–72.4) were also
improved at the end of the study 47.7 ± 15.2 mm
(95% CI 41.2–53.2). No significant changes were
seen in the other group’s QoL and VAS scores
(P > 0.05).

Figure 1 Comparison of (A) FEV1(lt), (B) FVC (lt), (C)
FEV1/FVC, (D) PEF (% predicted) in LTA (+) and LTA(–)
groups.

Figure 2 Comparison of (A) symptom, (B) impact, (C)
activity, and (D) total scores of SGRQ in LTA (+) and LTA
(–) groups.

Figure 3 Comparison of VAS results in LTA (+) and LTA
(–) groups.
The comparisons of the percent changes of the two groups had shown significant differences in all parameters except PEF (P < 0.05) (Table 2).

At the end of the study, there was a significant difference of PaO₂ in the montelukast group but there was no difference between the two groups of other ABG parameters.

None of the patients had exacerbations during the study period.

Also, during the study, sputum samples were obtained. 44 (37.6%) patients had sputum sample but 24 (20.5%) patients’ sputum were evaluated (13 in montelukast group, 11 in control group). Change in neutrophilic percentage before and after the study was seen in Table 3. Since the percentages of eosinophils were very low (2–3%), statistical analyses were not performed.

**Discussion**

The pathophysiology of airway obstruction in COPD is multifactorial, and involves neutrophilic airway inflammation,² protease–antiprotease imbalance,⁸ oxidative stress,⁹ T-cell predominant interstitial inflammation,¹⁰ and recurrent infection.¹¹ Analyses of bronchial biopsies, resected lung tissue, and induced sputum have shown that there is inflammation, even in the stable phase of COPD. These inflammatory processes in COPD are the reason for the use of anti-inflammatory therapy in COPD.

Based on the effectiveness of inhaled corticosteroids as anti-inflammatory agents in the treatment of asthma, the presence of mucosal inflammation in COPD is one rationale for their use in this condition. While the EUROSCOP and ISOLDE clinical trials have shown no beneficial effect of inhaled corticosteroids on the long term rate of lung function decline in COPD, they have shown significant improvement in FEV₁ over the first 3–6 months of treatment.¹²,¹³

The non-cysteinyl leukotriene, LTB₄ activates the B leukotriene receptor, while the cysteinyl leukotrienes (leukotriene C₄, leukotriene D₄, leukotriene E₄) activate cysteinyl leukotriene receptors 1 and 2 subtypes. A single class of receptors in human airway smooth muscle appears to mediate contractions induced by leukotriene C₄, leukotriene D₄, and leukotriene E₄. Although the most widely recognized of effects of leukotrienes is bronchoconstriction, leukotrienes also induce mucus secretion, inflammatory cell infiltration, microvascular permeability, airway smooth muscle proliferation, and neuronal input interactions.

Leukotriene receptor antagonists (such as montelukast, zafirlukast, etc.) inhibit leukotriene C₄ and leukotriene D₄ induced contractions in isolated airways,¹⁴ decrease leukotriene D₄ and leukotriene E₄ induced microvascular permeability,¹⁵ slow down the proliferation of airway smooth muscle,¹⁶ and have potential to decrease mucus production and increase mucus clearance.¹⁷

The first reported study about the use of LTA in COPD is the one of Cazzola in which they found a significant increase in FEV₁ of a small number of stable moderate to severe COPD patients after giving zafirlukast non-consecutively for 2 or 4 days.

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### Table 2  Comparison of percent change between LTA (+) and LTA (−) groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LTA (+) mean ± SD**</th>
<th>LTA (−) mean ± SD**</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>FVC</td>
<td>0.09 ± 0.23</td>
<td>0.05 ± 0.21</td>
<td>&lt;0.05⁴</td>
</tr>
<tr>
<td>FEV₁</td>
<td>0.17 ± 0.16</td>
<td>0.02 ± 0.12</td>
<td>&lt;0.05⁴</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.16 ± 0.26</td>
<td>0.12 ± 0.25</td>
<td>=0.05⁴</td>
</tr>
<tr>
<td>PEF</td>
<td>0.22 ± 0.49</td>
<td>0.34 ± 0.49</td>
<td>&gt;0.05⁴</td>
</tr>
<tr>
<td>Symptom score</td>
<td>−0.11 ± 0.17</td>
<td>0.1 ± 0.22</td>
<td>&lt;0.05⁴</td>
</tr>
<tr>
<td>Impact score</td>
<td>−0.26 ± 0.37</td>
<td>0.05 ± 0.25</td>
<td>&lt;0.05⁴</td>
</tr>
<tr>
<td>Activity score</td>
<td>0.25 ± 0.26</td>
<td>0.17 ± 0.18</td>
<td>&lt;0.05⁴</td>
</tr>
<tr>
<td>Total score</td>
<td>−0.25 ± 0.23</td>
<td>0.04 ± 0.17</td>
<td>&lt;0.05⁴</td>
</tr>
<tr>
<td>VAS</td>
<td>−0.5 ± 0.37</td>
<td>0.06 ± 0.11</td>
<td>&lt;0.05⁴</td>
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</table>

*Student’s t-test.
**[(Second month−basal)−basal].

### Table 3  Change in neutrophilic inflammation.

<table>
<thead>
<tr>
<th>Neutrophilic percentage</th>
<th>LTA(+) (n)</th>
<th>LTA(−) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Increased</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>No change</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

(Fisher’s exact test P = 0.059).
Cazzola mentioned that cysteinyl leukotrienes had particular bronchodilator effects in partially reversible COPD cases but added the lack of this effect on fixed airway obstruction. In another study concerning the short-term (within 2 h) efficacy of LTA, zafirlukast, in COPD patients with severe airway obstruction, anti-bronchoconstrictive or bronchodilator effect has been shown.

LTA montelukast's efficacy has been investigated in rats exposed to cigarette smoke and it has been found that leukotrienes can play a role in the pathogenesis of smoking-related lung diseases, and that montelukast may inhibit lung injury due to active and passive to cigarette smoking. In a long-term (2 years) retrospective study, Rubenstein showed a significant improvement in COPD control without any change in functional parameters in old, moderate to severe COPD patients.

In this study, we have investigated the short-term efficacy of LTA in stable patients with moderate to severe COPD, the two groups with or without LTA were compared according to PFT parameters, dyspnea scores, health-related QoL scores, ABG, and sputum neutrophil content. There was a significant increase in respiratory function parameters (FVC, FEV1, FEV1/FVC and PEF) in the group with LTA \( (P < 0.05) \).

SGRQ is one of the best detailed and standardized questionnaires in COPD. It consists of three parts as symptoms, impact and activity. When two groups in the study were compared in terms of these physical, psychycological and social parameters, the group with LTA had a decrease in all three scales of symptom, impact and activity \( (P < 0.05) \).

Dyspnea is the most frequently seen and complained symptom in COPD patients. This symptom is chronic, progressive, and deteriorates with disease progression. A good correlation between the scales used in the evaluation of dyspnea such as Medical Research Council (MRC), Baseline Dyspnea Index (BDI) and FEV1 has been reported. We used VAS in dyspnea evaluation and found a decrease in both groups but it was more significant in montelukast group \( (P < 0.05) \).

Airway inflammation in COPD can be demonstrated by the examination of sputum. Smokers and exsmokers with COPD have increased sputum neutrophil numbers compared with subjects without COPD, and increased neutrophils are associated with rapid decline in FEV1. Furthermore, the neutrophil activation markers, myeloperoxidase and lactoferrin, are elevated in the sputum of COPD subjects, indicating that neutrophils are active participants in airway inflammation. We could have done sputum analysis and evaluated the neutrophilic inflammation in 24 of the cases; the percent of neutrophils decreased by the treatment in montelukast group but this was not statistically significant as it was in the other clinical improvements obtained, probably due to the small number of patients \( (P = 0.059) \). Seventeen COPD patients had the leukotriene synthesis inhibitor BAY X1005 orally for 14 days and LTB4, myeloperoxidase and chemotactic activity were investigated in spontaneous sputum samples. There were no significant changes in the parameters mentioned above except for a decrease in LTB4 concentrations and the authors concluded that leukotriene synthesis inhibitors have caused a mild decrease in neutrophilic bronchial inflammation in COPD cases. It is clear that further studies including biochemical and molecular investigations on that aspect are needed.

The present study has many limitations; the impact of adding an LTA to routine protocols had been investigated but the solitary effect of inhaled corticosteroids had not been evaluated and the comparison of these two drugs had not been made. As far as we have seen, of these improvements with LTA, it would be worth of studying these aspects in further studies. The second limitation is the duration of the study in which we had evaluated the short-term effects but long-term outcomes such as emergency visit, the number and the duration of exacerbations could give different results. The improvements obtained in subjective parameters such as VAS and QoL and in the objective parameters such as functional tests had not been obtained in the inflammatory markers in sputum due to the small number of cases.

Despite the limitations mentioned above, the results of this particular study had been encouraging for the planning of further studies with LTA in COPD patients.

In conclusion, this study with montelukast in stable patients with moderate to severe COPD showed a significant improvement in respiratory functions, dyspnea scores, QOL Scores, and a non-significant improvement in sputum Scores and a non-significant improvement in sputum neutrophilia in the short term. The results of such studies showing improvements with anti-inflammatory treatment in COPD might make physicians consider these complementary drugs. Long-term, placebo-controlled studies with these drugs might make an impact on that aspect.

References


