Long-term montelukast therapy in moderate to severe COPD—a preliminary observation

Israel Rubinstein\textsuperscript{a,b,*}, Brijesh Kumar\textsuperscript{a,b}, Christopher Schriever\textsuperscript{c}

\textsuperscript{a}Department of Medicine (M/C 719), College of Medicine, University of Illinois at Chicago, 840 South Wood Street, Room 173, Chicago, IL 60612-7323, USA
\textsuperscript{b}VA Chicago Health Care System, Chicago, IL 60612, USA
\textsuperscript{c}Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612, USA

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Summary The purpose of this retrospective study was to determine the effects of long-term treatment with montelukast on chronic obstructive pulmonary disease (COPD) control in a cohort of patients with moderate to severe COPD. The medical records of 20 consecutive male patients (18 African-Americans) aged 71.2 ± 10.7 years diagnosed with moderate to severe COPD at the VA Chicago Health Care System, Chicago, Illinois, USA, and treated with oral montelukast, 10 mg every night, for 23.6 ± 7.3 months were reviewed. Information on demographics and COPD control was extracted from each record. In each patient, a comparable follow-up period in the clinic before and after initiating montelukast therapy was reviewed and tabulated so each patient served as his own control. There was a significant improvement in complaints of shortness of breath, sputum production wheezing and nocturnal symptoms during the observation period ($P < 0.05$). There was a significant reduction in the use of oral and inhaled corticosteroids, inhaled bronchodilators and supplemental oxygen ($P < 0.05$). In addition, there was a significant reduction in the number of visits to the emergency department, number of hospitalizations and duration of hospitalizations for acute exacerbations of COPD ($P < 0.05$). No significant changes in FEV$_1$ (% predicted), FEV$_1$/FVC ratio (% predicted) and peak expiratory flow rate were recorded during this time. No side effects were reported during the observation period and no patient discontinued the medication. Collectively, these data suggest that long-term treatment with montelukast is safe and improves COPD control in elderly patients with moderate to severe COPD.

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Introduction

Despite recent advances in medical therapeutics, treatment of patients with chronic obstructive pulmonary disease (COPD) remains largely symptomatic and, as such, represents an unmet medical need. \textsuperscript{1} This notion has important medical and socio-economic implications given that COPD is a
leading cause of chronic morbidity and mortality in the USA, and is predicted to rank fifth in worldwide burden of disease by the year 2020.²,³ Hence, there is an urgent need to develop and test new drugs that target pathophysiological mechanisms underlying COPD.⁴

To this end, cysteinyl leukotrienes (leukotriene C₄, D₄ and E₄) are potent pro-inflammatory mediators implicated in the pathogenesis of certain inflammatory lung diseases, including asthma.⁵,⁶ They have been shown to increase microvascular permeability, evoke mucus hypersecretion and elicit potent airway smooth muscle contraction.⁶ Some of these features are also present in the airway mucosa of patients with COPD.¹ It is well established that the concentrations of cysteinyl leukotrienes are increased in the sputum, plasma and circulating leukocytes of patients with COPD implying that they could play a role in the pathophysiology of this disorder.⁷⁻¹³ However, unlike certain patients with asthma, the effects of long-term therapy with cysteinyl leukotriene receptor antagonists on COPD control are uncertain.¹⁴⁻¹⁹

Hence, the purpose of this retrospective study was to begin to address this issue by determining the effects of long-term treatment with montelukast, a cysteinyl leukotriene receptor antagonist,⁶,¹⁸,²⁰ on COPD control in a cohort of elderly patients with moderate to severe COPD residing in inner-city Chicago.

**Methods**

**Patients**

The medical records of all patients with the diagnosis of moderate to severe COPD by established ATS criteria²¹ followed at the Chest Clinic of the VA Chicago Health Care System in Chicago and treated with oral montelukast, 10 mg every night, for at least 12 months were reviewed. All patients were ex-smokers (pack year, 43±2) and had irreversible airflow obstruction (increase in FEV₁ of <10% or <200 ml after inhaling a bronchodilator) on spirometry. They were non-smokers because every smoking patient attending the Chest Clinic is encouraged to quit smoking by clinic’s personnel. None reported a history of asthma or other respiratory disorders. Montelukast was prescribed at the discretion of the physician in the Chest Clinic when the patient’s respiratory complaints were no longer amenable to conventional therapy or shortly after recovering from an acute exacerbation of COPD.

Information about age, race, duration of COPD, self-reported symptoms of COPD, use of anti-COPD medications, duration of montelukast therapy, FEV₁ (% predicted), FEV₁/FVC ratio (% predicted), peak expiratory flow rate, number of visits to the emergency department for acute exacerbations of COPD, number of hospitalizations for an acute exacerbation of COPD, duration of hospitalization for an acute exacerbation of COPD and duration of follow-up at the outpatient clinic was retrieved from each record. In each patient, a comparable follow-up period in the clinic before and after initiating montelukast therapy was reviewed and tabulated so each patient served as his/her own control. The need for supplemental oxygen was gauged in each patient during clinic visits at rest and after walking in the clinic while breathing ambient air. Supplemental oxygen was discontinued or prescribed if transcutaneous oxyhemoglobin saturation was 90% and above or 88% and below, respectively.

A retrospective comparison of outcome measures between patients with moderate to severe COPD treated with montelukast to those who were not treated over the observation period was beyond the scope of this study. In addition, only spirometry was available for each patient to review so other parameters of pulmonary function, including arterial blood gases, are not reported. The study was approved by the Institutional Review Board.

**Data and statistical analyses**

Data are expressed as means±sd. Data were analyzed by Fisher’s exact test and Mann–Whitney U-test as indicated. Normality of distribution was analyzed with the Smirnov–Kolmogorov test and log transformation was used to normalize data distribution. A P<0.05 was considered statistically significant.

**Results**

Twenty male patients with moderate to severe COPD aged 71.2±10.7 years were enrolled in this study. Eighteen were African-Americans, one Caucasian and one Hispanic. All used inhaled bronchodilators daily, 12 patients were treated with prednisone on a regular basis, 15 used Inhaled corticosteroids daily some of which in combination with prednisone, and seven were using supplemental oxygen 24 h/day.
All 20 patients were treated with montelukast for 23.6 ± 7.3 months (range, 12–38 months). No adverse events to montelukast were recorded and no patient discontinued the drug during the observation period of this study. The characteristics of the patients before and after initiation of montelukast therapy are outlined in Table 1.

Long-term montelukast therapy was associated with significant improvement in self-reported shortness of breath, copious sputum production, wheezing and nocturnal symptoms (Table 1; P < 0.05). The decrease in self-reported shortness of breath from 95% before to 38% after initiation of montelukast therapy, and in copious sputum production from 80% before to 25% after initiation of montelukast therapy were particularly noteworthy. These salutary effects were associated with a significant reduction in regular use of prednisone, inhaled corticosteroids, inhaled bronchodilators and supplemental oxygen (Table 1; P < 0.05). The reduction in regular use of prednisone and inhaled corticosteroids was from 60% to 25% and from 75% to 44%, respectively (Table 1; P < 0.05).

Importantly, there was a significant reduction in the number of visits to the emergency department for acute exacerbations of COPD, number of hospitalizations for acute exacerbations of COPD, duration of hospitalization for acute exacerbations of COPD (Table 1; P < 0.05). There was no significant change in FEV1 (% predicted), FEV1/FVC ratio (% predicted) and peak expiratory flow rate during the observation period (Table 1; P > 0.5).

**Discussion**

The new finding of this study is that treatment with montelukast, 10 mg every night, for 12–38 consecutive months is associated with significant improvement in COPD control in elderly, predominantly African-American, patients with moderate to severe COPD residing in inner-city Chicago. The salutary effects of montelukast were noted in clinical, medication use, particularly prednisone and inhaled corticosteroids, and hospital visits and admissions for acute exacerbations of COPD over the observation period. By contrast, montelukast had no significant effects on FEV1, FEV1/FVC and peak expiratory flow rates, which are measures of central airway function, suggesting that it does not target the central airways of patients with moderate to severe COPD.

**Table 1** Characteristics of patients with moderate to severe COPD on long-term montelukast therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Montelukast Before</th>
<th>Montelukast After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>71.2 ± 10.7</td>
<td>—</td>
</tr>
<tr>
<td>Duration of COPD (yr)</td>
<td>9.9 ± 6.4</td>
<td>—</td>
</tr>
<tr>
<td>Duration of montelukast therapy (mo)</td>
<td>—</td>
<td>23.6 ± 7.3</td>
</tr>
<tr>
<td>Self-reported shortness of breath (%)</td>
<td>95</td>
<td>38*</td>
</tr>
<tr>
<td>Copious sputum production (%)</td>
<td>80</td>
<td>25*</td>
</tr>
<tr>
<td>Self-reported wheezing (%)</td>
<td>65</td>
<td>31*</td>
</tr>
<tr>
<td>Self-reported nocturnal symptoms (%)</td>
<td>25</td>
<td>6*</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>42 ± 18</td>
<td>40 ± 20</td>
</tr>
<tr>
<td>FEV1/FVC (% predicted)</td>
<td>57 ± 11</td>
<td>57 ± 17</td>
</tr>
<tr>
<td>PEFR (l/min)</td>
<td>218 ± 90</td>
<td>218 ± 86</td>
</tr>
<tr>
<td>Regular use of prednisone (%)</td>
<td>60</td>
<td>25*</td>
</tr>
<tr>
<td>Regular use of inhaled bronchodilators (%)</td>
<td>100</td>
<td>81*</td>
</tr>
<tr>
<td>Regular use of inhaled corticosteroids (%)</td>
<td>75</td>
<td>44*</td>
</tr>
<tr>
<td>Need for supplemental oxygen (%)</td>
<td>35</td>
<td>25*</td>
</tr>
<tr>
<td>No. of ED visits for AE of COPD (yr)</td>
<td>3.3 ± 2.8</td>
<td>1.2 ± 1.9*</td>
</tr>
<tr>
<td>No. of hospitalizations for AE of COPD (yr)</td>
<td>2.6 ± 2.3</td>
<td>0.9 ± 1.7*</td>
</tr>
<tr>
<td>Duration of hospitalization (days)</td>
<td>5.3 ± 5.5</td>
<td>1.7 ± 5.0*</td>
</tr>
</tbody>
</table>

Data are means ± sd; *P < 0.05 in comparison to before montelukast therapy; yr, year; mo, month; ED, emergency department; and AE, acute exacerbation.
moderate to severe COPD in which fixed airway obstruction predominates.\textsuperscript{1,14–16} Taken together, these data suggest that long-term (at least 12 months) montelukast therapy is associated with significant improvement in COPD control in elderly patients with moderate to severe COPD.

It is well established that airway inflammation characterized, in part, by increased microvascular permeability, mucus hypersecretion, neutrophil infiltration and tissue remodeling is present in patients with moderate to severe COPD.\textsuperscript{1,22} However, current therapeutic modalities recommended to circumvent this harmful and relentless process, including corticosteroids, do not target certain key components of the inflammatory cascade in the airway mucosa of patients with COPD, such as increased microvascular permeability and mucus hypersecretion.\textsuperscript{1,4,19,22} Moreover, unlike montelukast, they are froth with potentially serious adverse events, particularly among elderly individuals.\textsuperscript{4} Hence, there is an urgent need to develop and test new drugs that interrupt specific inflammatory pathways thought to play an important role in the pathophysiology of moderate to severe COPD.

The concentration of cysteinyl leukotrienes is increased in the sputum, plasma and circulating leukocytes of patients with COPD.\textsuperscript{7–13} To this end, Shindo et al.\textsuperscript{13} showed that circulating LTE\textsubscript{4} concentration increases significantly during acute exacerbations of COPD. Conceivably, elaboration of cysteinyl leukotrienes could play a role in the pathophysiology of airway inflammation in these patients. These data coupled with the results of the present study suggest that long-term administration of cysteinyl leukotriene receptor antagonists, such as montelukast, could be beneficial in patients with moderate to severe COPD. Alternatively, montelukast may express anti-inflammatory properties that are unrelated to its cysteinyl leukotriene receptor antagonism in patients with moderate to severe COPD. Additional studies are indicated to support or refute these hypotheses.

Cazzola et al.\textsuperscript{14,15} showed that zafirlukast, a cysteinyl leukotriene receptor antagonist, given for 2 or 4 non-consecutive days elicited a significant increase in FEV\textsubscript{1} in a small number of patients with stable moderate to severe COPD. The results of this study show that long-term (months) treatment with montelukast, 10 mg every night, is associated with significant improvement in COPD control with no appreciable change in FEV\textsubscript{1} in elderly predominantly African-American patients with moderate to severe COPD. The discrepant results between both studies are difficult to reconcile but may be related, in part, to differences in race, duration of treatment and perhaps inclusion of patients with COPD and a previously unrecognized history of asthma in the former.

The cellular origin of cysteinyl leukotrienes in the airway, the role of pro-inflammatory mediators elaborated by neutrophils and other cells through the 5-lipoxygenase activating protein (FLAP)/5-lipoxygenase metabolic pathway of arachidonic acid metabolism, such as leukotriene B\textsubscript{4}, were not elucidated in this study.\textsuperscript{23} To this end, Lee et al.\textsuperscript{22} showed that inhibitors of 5-lipoxygenase reverse neutrophil survival promoted by several pro-inflammatory mediators in patients with COPD in vitro. However, Gompertz and Stockley\textsuperscript{16} showed recently that 14-day therapy with a selective inhibitor of FLAP had only modest effects of certain parameters of inflammation in the sputum of patients with severe COPD. No other outcome measures were reported by these authors. Clearly, further studies using molecular, biochemical and cell biology techniques are warranted to address these issues.

The limitations of the present study are obvious. It is retrospective and encompasses only a relatively small number of predominantly African-American patients with moderate to severe COPD who were all ex-smokers. Hence, the applicability of the results of this study to a larger group of patients, and to patients with moderate to severe COPD who still smoke is uncertain. In addition, the improvement in COPD control was predominantly subjective, and the observed reduction in corticosteroids use during montelukast therapy might have been attributed to their lack of effectiveness in these patients. Nonetheless, the marked reductions in the number of visits to the emergency department for acute exacerbations of COPD, the number of hospitalizations for acute exacerbations of COPD and the duration of hospitalization for acute exacerbations of COPD are noteworthy. On aggregate, these data suggest that the salutary effects of long-term montelukast therapy in elderly patients with moderate to severe COPD could have been attributed, in part, to the drug. We propose that larger, multi-center, double-blind, randomized, placebo-controlled clinical trials should be contemplated to determine the efficacy of long-term montelukast therapy in smoking and ex-smoking patients with moderate to severe COPD.

In summary, we found that long-term (at least 12 months) montelukast therapy, 10 mg every night, is safe and associated with significant improvement in COPD control in elderly patients with moderate to severe COPD.
Acknowledgements

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References


