Marginal Utility of Montelukast for Persistent Asthma*

David A. Mathison, MD, and James A. Koziol, PhD

Background: The efficacy of a new pharmacologic agent for asthma, in this instance the leukotriene receptor antagonist montelukast, is determined in controlled trials in research subjects. The utility of a new drug is determined by multiple uncontrollable factors in individual patients.

Objective: To assess the utility of montelukast in the management of persistent asthma.

Design: Observational, retrospective.

Setting: Suburban multispecialty medical clinic.

Methods: From April 1998, montelukast was prescribed for 110 patients with persistent but controlled asthma, primarily for the corticosteroid-sparing effect. Outcomes after 1 year were determined from audits of medical records and responses to questionnaires.

Results: At least 56% of patients continued receiving montelukast for the entire year. However, compared to those patients who had discontinued montelukast therapy, those who continued receiving it had no difference in the use of inhaled or systemic corticosteroid or inhaled β₂-agonist therapy.

Conclusion: Montelukast had marginal utility in the management of these adult patients with controlled persistent asthma.

Key words: antiasthmatic agents; asthma; leukotriene antagonists; montelukast; outcomes assessment; patient

Prescription by physicians for a newly approved medication for asthma, in this instance the leukotriene receptor antagonist montelukast (Singulair; Merck & Co, Inc; West Point, PA), is based on evidence of efficacy in short-term, blinded, and controlled trials in selected and uniform cohorts of large numbers of compensated research subjects.¹,² The utility of a new medication depends on individual patient characteristics (e.g., severity of disease, cultural background, economic capabilities, adherence to prescribed regimen, dose route and frequency, palatability, and tolerability for side effects) in the aggregate, perceptions of benefit, and value leading to continued or discontinued use. This is a report on the utility of montelukast for persistent asthma based on observations of and by a series of 110 patients. As gauged by continued use after 1 year, > 56% of these patients found montelukast to have utility in the management of their asthma. As gauged by the concomitant use of other medications, montelukast had a marginal, if any, effect.

Materials and Methods

Over a 1-year period starting from its availability in April 1998, montelukast was prescribed for 110 patients with persistent asthma who were under continuing care by a single asthma specialist in a multispecialty physician group. Patients met the following criteria: they had persistent asthma, which was defined as the ongoing use of long-term control medication (e.g., corticosteroid, salmeterol, cromolyn/nedocromil, and/or theophylline); their disease was under control in terms of symptom control, optimal pulmonary function, and activity levels; and they were motivated to undertake a trial of new pharmacotherapy frequently by the wish to reduce corticosteroid usage. The majority of patients resided in outer-city and suburban San Diego, CA (women, 57%; men, 43%) with an age range of 11 to 88 years (median age, 53.5 years). More than ninety percent of patients had received a confirmation of their asthma by spirometric measurements of a response to an inhaled albuterol bronchodilator (mean FEV₁ rise, 29%) or to a methacholine bronchoconstrictor (mean FEV₁ fall, 32%); 84% of patients were atopic, as determined by positive responses to cutaneous or in vitro tests (pollen, 70%; house-dust mites, 54%; cats, 50%; mold, 45%; dogs, 35%; cockroach, 14%), and 15% of patients were aspirin-sensitive (i.e., had positive results to an oral challenge or a typical history).

On prescription (i.e., study entry) for montelukast (10 mg daily,
except doses of 5 mg daily for four patients under age 15 years), patients were instructed to continue individualized current programs of avoidance, immunotherapy, and medications. At follow-up contacts, patients who had continued to control their asthma, as indicated by no increase in the use of a rescue β-agonist inhaled bronchodilator and/or stable or improved FEV₁ values, were instructed to reduce corticosteroid use by approximately 20%.

One year after the initiation of montelukast therapy, medical records were audited by technicians for medication usage, including montelukast, and questionnaires sent to 103 patients (7 were lost to follow-up) were returned by 75 (73%) with responses relating to insurance coverage, perceived benefits, and side effects of the therapy. Patient anonymity was assured, and no experimental investigation was undertaken so that approval of the study by the Human Subjects Committee was not required. Inhaled corticosteroid use was quantitated in “fluticasone 220 equivalent puffs,” as noted in Table 1, and was calculated on the basis of individual use, as reported by the patient at their last visits for the years immediately preceding and subsequent to montelukast prescription. Systemic corticosteroid use was expressed as the average (including episodes of rescue use) daily dose of prednisone or its equivalent, as calculated for the years before and after entry. The use of short-acting and long-acting inhaled bronchodilators, cromolyn/nedocromil, and theophylline was noted for the last visits in the years before and after study entry. The details of our methods have been reported previously.4

Drug usage was summarized as the mean ± SE. Comparisons in drug usage between the two study cohorts (ie, continued vs discontinued montelukast usage) at corresponding time points were made with Wilcoxon tests for discrete data and standard two-sample t tests for continuous data. Comparisons within study cohorts of the amount of change (ie, differences in drug usage over the course of the 1-year observation period) were made with Wilcoxon signed-rank (discrete data) and paired-comparison t tests (continuous data). Observed two-sided p values of < 0.05 were taken to be indicative of statistical significance.

Results

As displayed in Table 2, 62 patients (or at least 56% of the patients) continued montelukast therapy and 37% discontinued montelukast therapy at 1 year (7% were lost to follow-up). The groups that continued and discontinued therapy did not differ for atopy/nonatopy, aspirin sensitivity, or insurance coverage for medications (patients continuing therapy, 96%; patients discontinuing therapy, 82%; p = 0.20). Side effects reported by seven patients included hives, dry mouth, and unspecified side effects. Six of the seven patients discontinued montelukast therapy.

The medication usage is summarized in Table 2. There were no statistically significant differences between the group that continued montelukast therapy and the group that discontinued montelukast therapy relating to therapy with inhaled β₂-agonists, inhaled salmeterol, inhaled corticosteroids, or systemic corticosteroids, either in the year preceding study or following study entry, or in the amount of change (ie, the difference in drug usage) over the 1-year period of observation. There was a statistically significant decline in inhaled β₂-agonist usage only in the group that continued montelukast therapy. On the other hand, inhaled corticosteroid usage declined only in the group that discontinued montelukast therapy, and both groups experienced statistically significant declines in systemic corticosteroid usage.

Discussion

The National Asthma Education and Prevention Program placed leukotriene-modifying drugs under consideration for the long-term control of mild, persistent asthma “although their position in therapy is not fully established.” The results of subsequent reports of direct comparisons of oral leukotriene receptor antagonists with inhaled corticosteroids and with inhaled long-acting β₂-agonist salmeterol suggest greater efficacy for the latter two agents, at least for adults. Nonetheless, one report suggested that montelukast therapy added to the control of asthma in subjects whose conditions were uncontrolled with low-dose beclomethasone therapy, and another report found that montelukast therapy.

![Table 1—Estimated Comparative Doses of Inhaled Corticosteroids Based on 1997 Guidelines for the Diagnosis and Management of Asthma*](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21973/)
Table 2—Medication Usage by Patients With Persistent Asthma

<table>
<thead>
<tr>
<th>Medication</th>
<th>Entire Group at Entry (n = 110)</th>
<th>Continued Montelukast (n = 62)</th>
<th>Discontinued Montelukast (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean (SE)</td>
<td>No.</td>
</tr>
<tr>
<td>Inhaled β₂-agonist, puffs/d</td>
<td>106</td>
<td>3.03 (0.35)</td>
<td>60</td>
</tr>
<tr>
<td>Inhaled salmeterol, puffs/d</td>
<td>50</td>
<td>3.66 (0.11)</td>
<td>30</td>
</tr>
<tr>
<td>Inhaled corticosteroids, fluticasone 220 equivalent puffs/d†‡</td>
<td>83</td>
<td>0.96 (0.10)</td>
<td>38</td>
</tr>
<tr>
<td>Systemic corticosteroids, mg/d‡</td>
<td>69</td>
<td>2.40 (0.33)</td>
<td>36</td>
</tr>
<tr>
<td>Cromolyn/nedocromil§</td>
<td>4</td>
<td>2.75 (0.53)</td>
<td>26</td>
</tr>
<tr>
<td>Theophylline‡</td>
<td>13</td>
<td>7.02 (0.02)</td>
<td>10</td>
</tr>
</tbody>
</table>

*Values given as mean (SE).
†Observed declines in medication usage (before − after) within the cohort (continued or discontinued montelukast therapy) statistically significant (p < 0.05).
‡Inhaled corticosteroid and systemic corticosteroid usage is further partitioned within each cohort into two subgroups whose usage did or did not decline to zero.
§Cromolyn/nedocromil and theophylline usage are summarized by the No. of patients using that medication in the year preceding study entry (before) and the No. of patients continuing to use that medication after the 1-year period of observation (after). The number of users was too small for precise dose change comparisons.

When compared to placebo, allowed a greater reduction in inhaled corticosteroid use in patients with chronic asthma who were receiving high doses of an inhaled corticosteroid. These reports reflect the results of pharmaceutical company-sponsored controlled trials of large numbers of highly selected research subjects. For example, Reiss et al3 enrolled 681 patients in order to have 95% power to detect a mean difference between treatment groups of 5.4 percentage points in FEV₁ (in terms of the percentage change from baseline). The extrapolation of results from such studies to individual patients cared for by physicians on a continuing basis requires monitoring and outcome audits for utility.

The differences between the results of this observational study and those of controlled trials lie in methodology, patient selection, and statistical power. The parameter of utility in patients with controlled asthma differs from measurements of asthma control outcomes in placebo or comparison controlled trials in research subjects with partially controlled asthma. The reductions of therapy with short-acting inhaled β₂-agonists and systemic corticosteroids coincident to the continuation of montelukast therapy over 1 year, compared to the discontinuation of montelukast therapy in this group of 110 patients, are modest. Prospectively, >500 patients would need to be observed in order to ensure that differences of this magnitude would be found to be statistically significant with a power of 0.90 at the two-sided 0.05 significance level. The results presented here are consistent with the results of the direct comparisons of therapy with leukotriene modifiers to inhaled corticosteroids and salmeterol. Unlike therapy with inhaled corticosteroids and salmeterol, the utility of therapy with montelukast has not been established as a long-term control medication for patients with persistent asthma.

REFERENCES

NetWorks

NetWorks Make the Difference…
You CanToo!

NetWorks are interdisciplinary, special interest groups providing the opportunity for personal involvement in the ACCP. NetWorks provide an outlet for action on a national level, establishing forums for advocacy, leadership, communication, and education. You can help make a difference by becoming involved in any one of the ACCP NetWorks. For more details on NetWorks, visit ChestNet at <www.chestnet.org/CHEST/2001/>.

Are you NetWorking yet?
Join the NetWork of your choice today!
e-mail: networks@chestnet.org
phone: Marla Brichta: 847-498-8364
Ellyn Shapiro: 847-498-8332

CHEST / 121 / 2 / FEBRUARY, 2002 337