Montelukast added to budesonide in children with persistent asthma: A randomized, double-blind, crossover study

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Objective: We tested the hypothesis that adding montelukast to budesonide would improve asthma control in children with inhaled glucocorticoid-dependent persistent asthma.

Study design: In a multicenter, randomized, double-blind, crossover study, we compared the benefit of adding montelukast, 5 mg, or placebo once daily to budesonide, 200 µg, twice daily.

Results: After a 1-month run-in with budesonide, 200 µg, twice daily, 279 children were randomized to montelukast or placebo. The mean ± SD age was 10.4 ± 2.2 years, the mean forced expiratory volume in 1 second (FEV₁) was 77.7% ± 10.6% predicted, and reversibility was 18.1% ± 12.9%. Compared with adding placebo to budesonide, adding montelukast produced significant improvements in mean percent change from baseline FEV₁ (P = .062 [P = .010 for per-protocol analysis]), mean absolute change from baseline FEV₁ (P = .040), mean increase from baseline in morning (P = .023) and evening (P = .012) peak expiratory flows, decrease in exacerbation days by approximately 23% (P < .001), decreased β₂-agonist use (P = .013), and reduced blood eosinophil counts (P < .001). The treatments did not differ significantly with regard to safety.

Conclusions: Montelukast, 5 mg, added to budesonide improved asthma control significantly, indicated by a small additive effect on lung function and a clinically relevant decrease in asthma exacerbation days. (J Pediatr 2001;138:694-8)

The orally administered cysteinyl leukotriene 1–receptor antagonist montelukast, which has both anti-inflammatory and bronchodilator effects, plays an increasingly important role worldwide in the management of persistent asthma and the prevention of exercise-induced bronchospasm.9,12 The beneficial effects of adding montelukast to inhaled glucocorticoid treatment, well documented in adults,13,14 have not yet been reported in children.

We hypothesized that the addition of 5 mg of montelukast to regular treatment with budesonide, 200 µg, twice daily through the Turbuhaler (Astra
Draco, Sweden) would improve the control of persistent asthma in young patients. We tested this hypothesis in a multicenter, randomized, double-blind, placebo-controlled, 2-treatment period, crossover study of 12 weeks’ duration.

**Methods**

**Participants**

The protocol was approved by the institutional review board of each participating center, and the parent or guardian of each child gave written informed consent. We studied nonsmoking children aged 6 to 14 years with persistent asthma who had been treated with inhaled glucocorticoid for at least 6 weeks before the study at doses of 200 to 800 µg daily of budesonide, beclomethasone dipropionate, triamcinolone acetonide, or flunisolide, or 100 to 500 µg daily of fluticasone propionate. During the run-in, despite treatment with 200 µg budesonide twice daily, as inclusion criteria, they were required to have forced expiratory volume in 1 second values of at least 60% and ≥60% of the predicted value (measured on at least 2 different visits), a ≥12% improvement in FEV₁ 20 to 30 minutes after short-acting β₂-adrenergic agonist administration (measured on at least 2 different visits), and asthma symptoms requiring a minimum average of at least 2 puffs per day of a β₂-adrenergic agonist in the 14 days immediately before randomization. Exclusion criteria were similar to those previously reported in a pediatric montelukast investigation.

**Treatment**

The study consisted of three 4-week periods. During period 1, children were prescribed open-label 200 µg budesonide twice daily through the Turbuhaler, and inclusion/exclusion criteria were evaluated. Short-acting β₂-adrenergic agonists were used as needed but were withheld for 6 hours before visits. All children demonstrated competence in peak flow meter and Turbuhaler use. During period 2, a double-blind active treatment period, eligible children were randomly assigned to receive a 5-mg chewable montelukast tablet or a matching placebo once daily at bedtime in addition to 200 µg of budesonide twice daily. During period 3, children treated with montelukast in period 2 received placebo, and vice versa. Children were seen at the beginning, middle, and end of each study period (every 2 weeks). There was no washout between study periods. End points were assessed only during the last 2 weeks of each active treatment period.

**End Points**

The primary end point was percent change in FEV₁ from baseline, measured with a Puritan-Bennett PB100 Spirometer (Wilmington, Mass). Nurses and technicians were trained at a central site. Tests were performed at the same time ±2 hours each study day, and spirometric tracings were evaluated with American Thoracic Society criteria for acceptance. A secondary end point, peak expiratory flow, was monitored at home twice daily with an AirWatch (LifeChart.com, Inc, Mountain View, Calif). Other secondary end points included asthma exacerbation and attack rates, β₂-adrenergic agonist use, physician and parent global assessments, quality-of-life measures, and peripheral blood eosinophil counts. The parents (and children aged 9 and older) recorded the medications used each day in a diary, which was reviewed during clinic visits. Asthma attacks were defined as worsening asthma requiring an unscheduled visit to a physician or an emergency department, hospitalization, or treatment with oral glucocorticoids. Exacerbation days were defined as one occurrence of any of the following: decrease from baseline peak flow of >20%, increase from baseline in β₂-adrenergic agonist use of >70% (minimum increase of ≥2 puffs), or an asthma attack (defined previously). Adherence to treatment with montelukast and placebo was assessed by tablet counts and review of diaries.

Clinical adverse experiences were evaluated throughout the study in terms of severity (mild, moderate, or severe), duration, seriousness, outcome, and relationship to study medications. Laboratory tests included complete blood counts, liver function tests and other blood chemistry tests, and electrocardiograms.

**Statistical Analysis**

The primary efficacy end point was percent change from baseline (week 4) in FEV₁ values averaged over the last 2 visits of the treatment period. The percent change from baseline in FEV₁ from the 2 periods of the crossover study was assessed by an analysis of variance for the within-patient treatment contrasts. The mean treatment difference was adjusted for a period effect, and possible carryover effects were assessed.

Both intention-to-treat analysis (primary analysis) and a per-protocol analysis for the primary end point only (based on prespecified rules) were performed. The per-protocol analysis excluded children with important protocol deviations such as baseline FEV₁ >90% predicted, lack of improvement in FEV₁ after bronchodilator use during the run-in period, use of oral glucocorticoids, lack of withholding β₂-adrenergic agonists before visits, and noncompliance with montelukast or placebo (>50% missed doses).

End points other than FEV₁ were also assessed by an analysis of variance for the within-patient differences. The last 2 weeks of values were used for peak expiratory flows and β₂-agonist use. For quality-of-life, changes from baseline (week 4) versus the end of each treatment period were used.

Statistical significance was accepted with a P value of ≤.05. The study was planned with 200 patients to have 95% power (α = .05) to detect a 4.4 percentage point difference in FEV₁.
RESULTS

Participants

A total of 279 children with asthma were randomized to receive either montelukast or placebo initially. The mean age (SD, range) was 10.4 years (2.2, 5 to 15), and the mean height was 144 cm (14, 109 to 182); 67% of the children were boys, 83% were white, 10% were Asian, 6% were Hispanic, and 1% were members of other ethnic groups. At baseline their mean FEV\(_1\) (SD) was 1.8 L (0.6), mean FEV\(_1\) % predicted was 77.7 (10.6), post-albuterol FEV\(_1\) was 2.1 L (0.6), and post-albuterol FEV\(_1\) % predicted was 89.7 (11.7), with a mean FEV\(_1\) reversibility of 18.1% (12.9). The mean morning peak expiratory flow (SD) was 315 (130) L/min. The mean \(\beta_2\)-adrenergic agonist use (SD) was 2.9 (2.0) puffs per day. The 2 sequence groups were well matched with respect to demographics and baseline values.

Attrition of Participants

Of the 279 randomized children, 264 (95%) completed the study; 7 were discontinued because of deviation from the protocol, 3 because of clinical adverse events and 5 for miscellaneous reasons. A total of 251 (90%) children were included in the primary efficacy analysis of percentage change from baseline in FEV\(_1\); 15 had data excluded because of oral glucocorticoid use, 9 were discontinued before crossover, and 4 used montelukast and placebo concomitantly.

A total of 205 (73%) children were included in the per-protocol analysis of the primary end point. The most common reasons for excluding children from this analysis were a baseline FEV\(_1\) >90% of the predicted value (21 children), oral glucocorticoid use in 15 children (as previously described), FEV\(_1\) reversibility not ≥10% on 2 occasions in 7 children, and baseline \(\beta_2\)-adrenergic agonist use <0.5 puffs per day in 9 children.

Efficacy

There was a significant mean percentage increase from baseline in FEV\(_1\) for both montelukast and placebo (\(P \leq .001\)) over the double-blind treatment period (Fig 1). The mean percentage increase in FEV\(_1\) during montelukast treatment was 4.6%, and during placebo treatment it was 3.3% (difference of 1.3 percentage points with 95% CI: –0.1 to 2.7, \(P = .062\)). In the per-protocol analysis the mean percentage increase in FEV\(_1\) during montelukast treatment was 6.0% and during placebo treatment 4.1% (difference of 1.9 percentage points 95% CI: 0.5 to 3.4, \(P = .01\)). There was significant improvement in morning and evening peak expiratory flows monitored at home, averaged over the last 14 days of each double-blind treatment period. The montelukast versus placebo difference was 9.7 L/min for morning peak flow (95% CI: 1.4 to 18.1, \(P = .023\)) and 10.7 L/min for evening peak flow (95% CI: 2.4 to 19.0, \(P = .012\)). Improvement in peak expiratory flows was noted on the first day of treatment, as indicated by a morning peak flow increase from baseline of \(\approx\)25 L/min for montelukast versus \(\approx\)12 L/min for placebo.

During both treatments there was a significant decrease from baseline in average \(\beta_2\)-adrenergic agonist use (\(P \leq .001\)) (Fig 2), from 3.01 puffs per day at baseline to 1.65 puffs per day with montelukast (a decrease of 1.36 puffs per day) and to 1.98 puffs per day with placebo (a decrease of 1.03 puffs per day). The mean decrease in \(\beta_2\)-adrenergic agonist use was significantly (\(P = .013\)) greater for montelukast compared with placebo. The mean percentage of asthma exacerbation days was lower during montelukast treatment than during placebo treatment (\(P <
12.2% for montelukast compared with 15.9% for placebo. Baseline value for quality-of-life measurement was 5.46 for all children. After montelukast treatment, this improved to 6.0 (SD 0.97) (P \leq 0.001), and after placebo treatment, it improved to 5.91 ± 0.93 (P \leq 0.001); the effects of montelukast and placebo did not differ significantly. There was no significant difference between treatment groups in global evaluations or asthma attacks.

Blood eosinophil counts decreased by 15% (from 0.476 to 0.404 × 10^9/L) for montelukast compared with an increase of 7% (from 0.478 to 0.510 × 10^9/L) for placebo (P < 0.001). Adherence, assessed with tablet counts for montelukast and placebo, was 96.4%.

**Safety**

There was no significant difference between the 2 treatments with respect to the overall incidence of clinical or laboratory adverse experiences. The overall incidence of clinical adverse experiences was 42% for montelukast and 45% for placebo. The most common adverse experiences (incidence ≥4%) were asthma worsening, upper respiratory tract infection, headache, cough, pharyngitis, and fever (Table). The incidence of clinical adverse experiences that were possibly, probably, or definitely related to study medication for all randomized patients was 3% during both montelukast and placebo treatment. Three patients discontinued study medication because of clinical adverse experiences: 1 receiving montelukast treatment and 2 receiving placebo treatment. No medication-related serious adverse experiences were reported.

**DISCUSSION**

In children with inhaled glucocorticoid-dependent persistent asthma who had symptoms despite administration of 200 µg of budesonide twice daily, montelukast improved the mean percent increase from baseline in FEV₁ and morning and evening peak expiratory flows and decreased asthma exacerbation days despite a concomitant decrease in β₂-adrenergic agonist use. Its anti-inflammatory effect, suggested by the significant reduction in blood eosinophils, has been documented directly in other asthma studies, in which decreased eosinophils in induced sputum and bronchial biopsy specimens and decreased nitric oxide in exhaled air have been reported.

The subjective and objective improvements in asthma produced by adding montelukast to inhaled budesonide, although modest, were consistently and significantly greater than the amount of improvement produced by placebo, despite the substantial placebo response. They cannot be attributed to lack of adherence with montelukast treatment, which was >95% throughout, or to the children being too well despite taking 200 µg of budesonide twice daily during run-in, because during this time, they had a mean reversibility of 18.1% ± 12.9% (range up to 85.6%). When the study was designed, a total daily budesonide dose of 400 µg was considered to be a low dose, although it is now recognized as being near the top of the dose-response curve for this inhaled glucocorticoid.

Our study extends the information obtained in a double-blind, placebo-controlled, 8-week study in children aged 6 to 14 years with a mean FEV₁ of 72% predicted at entry, in which those taking montelukast had a significantly greater improvement in FEV₁ from baseline compared with those taking placebo (8.23% vs 3.58%). Also, our results are consistent with those from clinical trials in adults, in which 10 mg of montelukast daily had an additive effect when administered with an inhaled glucocorticoid and maintained asthma control during glucocorticoid tapering.

Taken together, these findings substantiate the recommendations that the addition of an oral cysteinyl leukotriene receptor antagonist to an inhaled glucocorticoid should be considered in any child in whom the inhaled glucocorticoid alone does not provide full control of persistent asthma. The two different classes of medication would be expected to have an additive effect because the anti-inflammatory effects of leukotriene modifiers complement those of glucocorticoids.

Other options suggested for addition to the treatment regimen of patients with moderate-to-severe persistent asthma who have symptoms despite inhaled glucocorticoid treatment include long-acting β₂-adrenergic agonists or theophylline. The added beneficial effects of these medications when given with inhaled corticosteroids have been demonstrated more convincingly in adults than in children. The relative advantages and disadvantages of adding a leukotriene modifier, a long-acting β₂-adrenergic agonist, or theophylline to inhaled glucocorticoid treatment in children require investigations similar to the one underway in adults.
In summary, montelukast provides significant added benefits when administered concurrently with budesonide to children. Although its additive effects on lung function are small, it leads to a reduction of approximately 23% in exacerbation days, which is clinically relevant.

We thank Ms Veerle Coenen for data coordination and Ms Pam Dellea for study coordination.

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tomelukast/additivity study group also included: Dr M. Grenville (Argentina); Dr P. W. J. Francis, J. Martin, C. Robertson, and N. Freezer (Australia); Drs E. Eber and E. Horak (Austria); Dr N. A. R. Filho and J. M. A. Cardieri (Brazil); Dr S. Spier and B. Mazier (Canada); Dr J. De Blic (France); Dr G. Kasenbach, T. Zimmer
mann, J. Kuhn, M. Silbermann, B. Schmomm, S. Wegner, P. Lauch, S. Knappe, and P. Po
tlaczk (Germany); Dr P. A. Papageorgiou and A. Constantopoulos (Greece); Dr M. Pette
toren, J. I. Holme, T. Y. Halvorson, and D. Bjamer (Norway); Dr M. De Lariko N. Chiera and M. Queirou (Portugal); Dr G. Hattievig and G. Hellin (Sweden); Dr J. C. De Jonge (The Netherlands); Dr B. M. Bekkum and A. G. Chuchalbin (Russia); and Dr Y. Saradac (Turkey).

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