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# Formoterol, montelukast, and budesonide in asthmatic children: Effect on lung function and exhaled nitric oxide

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## Summary

**Background:** It has been proposed that asthma control may be achieved in part by minimizing airway inflammation. The simultaneous effects of inhaled steroids associated with long-acting  $\beta$ -agonists and leukotriene antagonists on pulmonary function and airway inflammation are still largely unexplored in children with moderate persistent asthma.

**Objectives:** The aim of this study was to investigate the effects of add-on therapy with long-acting  $\beta$ -agonists and leukotriene antagonists on FEV<sub>1</sub> and exhaled nitric oxide levels (FE<sub>NO</sub>) in children.

**Methods:** Forty-eight steroid-naïve atopic asthmatic children, 7–11 years of age, were randomly treated in four groups for two consecutive one-month periods, as follows: (1) first month: budesonide 200  $\mu$ g twice daily; second month: budesonide 400  $\mu$ g twice daily; (2) first month: budesonide 200  $\mu$ g twice daily+formoterol 9  $\mu$ g twice daily; second month: budesonide 200  $\mu$ g twice daily+montelukast 5 mg once daily; (3) first month: budesonide 200  $\mu$ g twice daily+montelukast 5 mg once daily; second month budesonide 200  $\mu$ g+formoterol 9  $\mu$ g twice daily; (4) first and second month: budesonide 400  $\mu$ g twice daily.

**Results:** All treatments resulted in a significant increase in lung function and a decrease in FE<sub>NO</sub> compared with values at baseline. Budesonide+montelukast in combination was the most effective treatment for reducing FE<sub>NO</sub> levels.

**Conclusion:** This study demonstrates that add-on therapy with montelukast plus low-dose budesonide is more effective than the addition of long-acting  $\beta$ -agonists or doubling the dose of budesonide for controlling FE<sub>NO</sub> in asthmatic children.

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**Abbreviations:** BD, budesonide; FE<sub>NO</sub>, exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; FM, formoterol; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; LTRA, leukotriene antagonist; MK, montelukast.

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## Introduction

The evidence that asthma is a chronic inflammatory disease of the airways supports the regular use of an anti-inflammatory treatment, even in patients with mild persistent disease.<sup>1</sup> Currently, inhaled corticosteroids (ICS) represent the most effective anti-inflammatory treatment for the majority of asthmatic patients with persistent asthma.<sup>1</sup> Nevertheless, potential side effects of long-term treatment with high daily dosages have to be considered, particularly in children. Based on this issue, the most recent revisions of international guidelines for asthma management suggest an add-on therapy with either long-acting  $\beta_2$ -agonists (LABAs) or leukotriene antagonists (LTRAs) as an alternative to an increased dose of ICS in adults and children with moderate persistent asthma.<sup>1</sup> However, LABAs and LTRAs are characterized by markedly different pharmacologic properties that could provoke substantially different effects on the basic mechanisms of the disease,<sup>2,3</sup> which are largely unexplored in children.<sup>4</sup>

Exhaled nitric oxide ( $FE_{NO}$ ) is considered a valid parameter for a non-invasive monitoring of airway inflammation<sup>5-8</sup> and it has been shown to be a useful marker for assessment of pharmacologic therapy for airway inflammation.<sup>9</sup> Recently, it was shown that measurements of  $FE_{NO}$  levels may be used to guide treatment of asthma.<sup>10</sup> The aim of this study was to investigate whether the different treatment options proposed by international guidelines for children with moderate asthma are comparable in controlling the disease, not only in terms of improving lung function but also improving airway inflammation, as measured by  $FE_{NO}$  levels.

## Methods

### Subjects

Fifty-one steroid-naïve atopic asthmatic children (27 girls and 24 boys), from 7 to 11 years of age, attending the Pediatric Department of Second University of Naples (Italy), were screened in this study. All patients were sensitized to house dust mites and met the criteria for the American Thoracic Society definition of asthma.<sup>11</sup> All children demonstrated an increase of at least 12% in forced expiratory volume in 1s ( $FEV_1$ ) after administration of 200  $\mu$ g of salbutamol and were classified as moderate, persistent asthmatics.<sup>1,11</sup> A medical history was collected and children underwent a physical examination, spirometry with reversibility to  $\beta_2$ -agonists,  $FE_{NO}$  measurement, and skin prick test to the most common allergens. Three children were unable to comply with one or more tests; therefore, 48 children were admitted to the study. The study was performed out of season for seasonal allergens to avoid the confounding effect of such exposure. Patients had not received oral or ICS, LABAs, or LTRAs for at least 4 weeks before admission to the study; the only treatment used during that period was inhaled salbutamol. Children also did not use  $\beta_2$ -agonists within the 24-h period before lung capacity measurements.

The protocol had the ethical approval by the second University of Naples, and all subjects signed informed consent.

### Study design

This was a double-blind study in which 48 patients were randomly allocated into one of four parallel groups of 12 patients each for two consecutive one-month periods, as follows: (1) first month: budesonide (BD) 200  $\mu$ g twice daily; second month: budesonide 400  $\mu$ g twice daily (BD 400/BD 800 group); (2) first month: budesonide 200  $\mu$ g twice daily+formoterol (FM) 9  $\mu$ g twice daily; second month: budesonide 200  $\mu$ g twice daily+montelukast (MK) 5 mg once daily (BD 400+FM/BD 400+MK group); (3) first month: budesonide 200  $\mu$ g twice daily+montelukast 5 mg once daily; second month budesonide 200  $\mu$ g+formoterol 9  $\mu$ g twice daily (BD 400+MK/BD 400+FM group); (4) first and second month: budesonide 400  $\mu$ g twice daily (BD 800/BD 800 group). Since this was a spontaneous study with no support of pharmaceutical industry and without official placebos or study-dedicated preparations, in order to keep the patients and the clinical investigators blind about the regimen of treatment, the following procedures were undertaken. Budesonide and formoterol Turbuhaler dedicated to the study were prepared by a doctor not involved in the clinical part of the study. The devices were unlabelled, those dedicated to placebo formoterol were carefully emptied and the reservoirs cleaned by suctioning with a vacuum pump. A non-matching placebo for montelukast was obtained by preparing a dedicated small sweet cherry-tasting candy with a very similar shape, colour and taste of the active drug. Furthermore, the patients had never experienced before neither budesonide/formoterol nor montelukast treatment and therefore were unable to distinguish between active drug or placebo. An external doctor (not participating to the evaluation of the patients) prepared the study drugs and placebos, as well as the randomization table. The parents received sealed packages containing the study drugs, i.e. budesonide at one of the above referred concentrations and either the combination of active formoterol plus placebo montelukast or placebo formoterol plus active montelukast. The sealed packages were delivered when the patients had left the hospital and they had returned the used drugs to the doctor who prepared the packages, in order to keep the clinical investigators blind about the treatment regimen for each patient. A treatment randomization list was kept in a sealed envelope in order to know the allocation of every patient in the case of emergency.

Patients visited the clinic three times: immediately before initiation of treatment, at the end of the Month 1, and at the end of Month 2. At each visit,  $FE_{NO}$  and spirometric measurements were performed.

### Nitric oxide measurement

$FE_{NO}$  was measured with a chemiluminescence analyzer (Model 280 Nitric Oxide Analyzer, Severs Instrument Inc., Boulder, CO); the detection limit of the apparatus was 1–5 parts per billion (ppb), as required by ATS guidelines, with a

resolution of 1 ppb. The analyzer was calibrated daily, using a certified NO mixture. Exhaled NO was recorded with the singlebreath method according to published guidelines.<sup>12</sup> Children inhaled to total lung capacity from NO-free air and exhaled a single breath (without nose clip) through a mouthpiece at a mouth pressure of > 5 cm water and at an expiratory flow of 50 mL/s. Mouth pressure was displayed on a computer screen as a prompt for the children to maintain a steady flow. The measurement was rejected if a stable flow was not maintained for at least 6s of exhalation. Nitric oxide was measured at the plateau and expressed in ppb.

**Lung function and reversibility test**

Following FE<sub>NO</sub> measurements, lung function variables forced vital capacity (FVC) and FEV<sub>1</sub> were measured using a dry spirometer (Vmax series 22; Sensormedics) according to published guidelines.<sup>13</sup> The best value of three measurements was recorded and expressed as a percentage of the predicted value. The reversibility test requires an increase of more than 12% in FEV<sub>1</sub> compared with baseline 15 min after inhalation of 200 µg salbutamol delivered by metered dose inhaler.

**Statistical analysis**

Results for FE<sub>NO</sub> and FEV<sub>1</sub> are reported as means ± standard errors of the mean. Analysis of variance (ANOVA) was used to compare FE<sub>NO</sub> and spirometric values between and within groups. Significance was declared when *P* < 0.05.

**Results**

There were no significant differences in mean baseline FE<sub>NO</sub> and FEV<sub>1</sub> among the four treatment groups (Tables 1 and 2).

BD 400/BD 800 group: After one month of treatment with budesonide twice daily at 200 µg, mean FE<sub>NO</sub> decreased from 39.9 ± 0.8–28.3 ± 0.9 ppb (*P* < 0.01) (Fig. 1B). At the end of Month 2 (twice-daily treatment with 400 µg budesonide), FE<sub>NO</sub> was 25.5 ± 1.1 ppb. The change is FE<sub>NO</sub> from the end of Month 1 to the end of Month 2 was not significant. Mean FEV<sub>1</sub> increased from 76.2% ± 2.5% of predicted at baseline to 84.1% ± 2.4% at the end of Month 1 and to 86.7% ± 2.4% at the

**Table 1** FEV<sub>1</sub> Group A: 1st month budesonide (bud) 200 mcg/bid and 2nd month bud 400 mcg/bid; Group B: 1st month, bud 200 mcg/bid+formoterol 9 mcg/day; 2nd month: bud 200 mcg/bid+montelukast 5 mcg/day; Group C: 1st month: bud 200 mcg/bid+montelukast 5 mcg/day; 2nd month bud 200 mcg/bid+formoterol 9 mcg/day; Group D: for two months were administered bud 400 mcg/bid. T0: basal value T1: after the first month of treatment T2: after the second month of treatment.

	T0	T1	T2
Group A	76.2 ± 8.7	84 ± 8.4	86.6 ± 11
Group B	75.3 ± 7	94.2 ± 11.9	95.7 ± 12.8
Group C	77 ± 7.5	95.6 ± 10.5	97 ± 10.4
Group D	79 ± 5.9	86 ± 5.5	89 ± 5.6

**Table 2** FE<sub>NO</sub> Group A: 1st month budesonide (bud) 200 mcg/bid and 2nd month bud 400 mcg/bid; Group B: 1st month, bud 200 mcg/bid+formoterol 9 mcg/day; 2nd month: bud 200 mcg/bid+montelukast 5 mcg/day; Group C: 1st month: bud 200 mcg/bid+montelukast 5 mcg/day; 2nd month bud 200 mcg/bid+formoterol 9 mcg/day; Group D: for two months were administered bud 400 mcg/bid. T0: basal value T1: after the first month of treatment T2: after the second month of treatment.

	T0	T1	T2
Group A	39.9 ± 2.9	28.3 ± 3.2	25.3 ± 3.8
Group B	38 ± 3.7	24.8 ± 3.2	18.1 ± 3.7
Group C	38.7 ± 4.3	19 ± 3.8	25.2 ± 3.9
Group D	41.1 ± 4.5	27 ± 4.5	27.7 ± 4.7

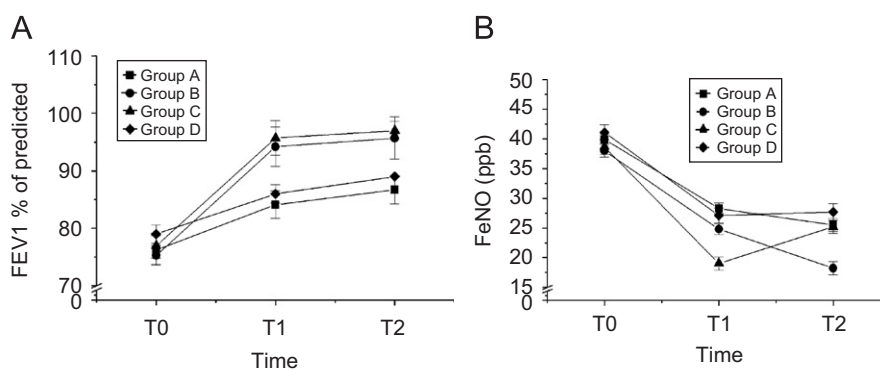
end of Month 2 (Fig. 1A). The increase from baseline to the end of Month 2 was significant (*P* < 0.05).

BD 400+FM/BD 400+MK group: Mean FE<sub>NO</sub> decreased from 38.0 ± 1.1 ppb at baseline to 24.8 ± 0.9 ppb at the end of Month 1 (*P* < 0.01) for children treated with budesonide 200 µg+formoterol 9 µg twice daily (Fig. 1B). After switching to budesonide 400 µg twice daily+montelukast 5 mg once daily, mean FE<sub>NO</sub> further decreased to 18.2 ± 1.1 ppb (*P* < 0.01) at the end of Month 2. Mean FEV<sub>1</sub> increased from 75.3% ± 1.7% of predicted at baseline to 94.2% ± 3.4% at the end of Month 1 (*P* < 0.05) and further increased to 95.7% ± 3.7% at the end of Month 2 (Fig. 1A). The increase from baseline to the end of Month 2 was significant (*P* < 0.01).

BD 400+MK/BD 400+FM group: FE<sub>NO</sub> mean values decreased significantly from 38.7 ± 1.3 ppb at baseline to 19.0 ± 1.1 ppb (*P* < 0.01) at the end of Month 1 (budesonide+montelukast), whereas it increased to 25.2 ± 1.1 ppb (*P* < 0.05) at the end of Month 2 after 1 month of treatment with budesonide+formoterol (Fig. 1B). Mean FEV<sub>1</sub> increased from 77.0% ± 2.2% of predicted to 95.7% ± 3.0% at the end of Month 1 (*P* < 0.05) and to 97.0% ± 1.6% at the end of Month 2 (Fig. 1A). The increase from baseline to the end of Month 2 was significant (*P* < 0.01).

BD 800/BD 800 group: After one month of therapy with budesonide 400 µg twice daily, mean FE<sub>NO</sub> decreased from 41.1 ± 1.3 ppb to 27.1 ± 1.3 ppb (*P* < 0.01) (Fig. 1B). Little change was noted after the second month of treatment with budesonide 400 µg (27.7 ± 1.4 ppb). The change from baseline to the end of Month 2 was significant (*P* < 0.01). At the end of one month, mean FEV<sub>1</sub> increased from 79.0% ± 1.6% of predicted to 86.0% ± 1.6% (Fig. 1A). At the end of Month 2, mean FEV<sub>1</sub> had increased to 89.0 ± 1.6%. The increase from baseline to the end of Month 2 was significant (*P* < 0.05).

Between-group comparisons: Mean FE<sub>NO</sub> was significantly lower after one month of treatment for children who had received budesonide+montelukast (BD 400+MK/BD 400+FM group) versus all other groups (*P* < 0.001). Mean FEV<sub>1</sub> for this treatment regimen also was significantly higher at the end of one month of treatment compared with the value for the BD 400/BD 800 group treated twice daily with budesonide 200 µg.



**Figure 1** Changes in FEV<sub>1</sub> (panel A) and in FE<sub>NO</sub> (panel B) for the four groups of children (mean+standard error). Group A: 1st month budesonide (bud) 200 mcg/bid and 2nd month bud 400 mcg/bid; Group B: 1st month, bud 200 mcg/bid+formoterol 9 mcg/day; 2nd month: bud 200 mcg/bid+montelukast 5 mcg/day; Group C: 1st month: bud 200 mcg/bid+montelukast 5 mcg/day; 2nd month bud 200 mcg/bid+formoterol 9 mcg/day; Group D: for two months were administered bud 400 mcg/bid. T0: basal value T1: after the first month of treatment T2: after the second month of treatment. For statistical significance please refer to the result section of the text.

At the end of Month 2, the BD 400+FM/BD 400+MK group treated with budesonide+montelukast had a significantly greater decrease in FE<sub>NO</sub> than did the other groups ( $P < 0.001$ ). No significant difference was observed for FEV<sub>1</sub> among treatment groups at this evaluation time.

## Discussion

The present study demonstrated how the addition of montelukast to low dose (200 mcg bid) budesonide is able to induce an adjunctive effect on FE<sub>NO</sub> reduction as compared to both higher dosage (400 mcg bid) of budesonide and add-on therapy of formoterol to low dose budesonide.

Previous studies comparing the effect of LABAs with LTRAs in asthmatic patients not controlled by ICS alone determined a better effect with the addiction of LABA.<sup>14–16</sup> Nevertheless, a recent study in a large population of patients uncontrolled by ICS alone reported a better response to rescue medication and control of exercise-induced symptoms with montelukast than with salmeterol.<sup>17</sup> A recent meta-analysis of results up to the beginning of 2004 concluded that, in asthmatic adults for whom an add-on treatment to low-dose ICS was required, LABAs were superior to LTRAs in preventing asthma exacerbations, improving lung function, symptoms, and reducing in the use of rescue medications.<sup>18</sup> Most of the available comparative studies, including those considered in the meta-analysis,<sup>18</sup> are based on lung function or symptom reports. However, previous reports have demonstrated that these LABAs and LTRAs are characterized by substantially different effects on FE<sub>NO</sub>.<sup>2,3</sup> In fact, whereas LABAs have been shown to have no effect on FE<sub>NO</sub> in children with mild asthma,<sup>19</sup> montelukast was able to reduce FE<sub>NO</sub> when it was used either as a monotherapy<sup>20</sup> or added to ICS.<sup>21</sup> More recently, Buchvald et al.<sup>22</sup> have compared the effects of salmeterol versus montelukast add-on therapy on FE<sub>NO</sub> in asthmatic children undergoing regular maintenance treatment with a daily dose of 400 mcg of budesonide. Studies show that levels of FE<sub>NO</sub> were higher after the addition of salmeterol, as compared with either placebo or montelukast.<sup>22</sup>

Several reports have emphasized the importance of assessing airway inflammation in designing appropriate therapeutic strategies for asthma control. Green et al.<sup>23</sup> showed that a greater reduction in asthma exacerbation was achieved by minimizing eosinophilic airway inflammation rather than by following standard care. Measurement of FE<sub>NO</sub> levels has been proposed as a practical guide to treating asthma.<sup>24</sup> In the present study, if we consider the changes in FE<sub>NO</sub> with those observed for FEV<sub>1</sub> in the two groups with add-on therapy we might speculate that these parameters are differently influenced by the therapeutic strategies. In fact, FE<sub>NO</sub> and FEV<sub>1</sub> improved significantly for two groups treated with add-on therapy (groups B and C) in the first period of treatment. In the second phase of the study, instead only the changes in FE<sub>NO</sub>, but not in FEV<sub>1</sub> reflect the switching effect from the therapeutic options. The FEV<sub>1</sub> changes observed after the first month only in the groups treated with either formoterol or montelukast confirm that in montelukast has a positive effect on lung function in children as recently demonstrated by two studies by Straub.<sup>22,23</sup> The data from the present study regarding FEV<sub>1</sub> variations during treatment are partially in contrast with those presented by Buchvald et al.<sup>22</sup> In fact, in that study, the group treated with LABA was the only one with significant increase in FEV<sub>1</sub>, whereas the present data suggest that both formoterol and montelukast were able to induce an increase in FEV<sub>1</sub> at T1. However, when comparing the two studies in terms of lung function, the main difference is represented by the baseline level of FEV<sub>1</sub>, being 101% of predicted in children participating to Buchvald's study<sup>22</sup> (treated with 400 mcg/d maintenance dose of inhaled budesonide at the time of admission) in contrast to levels below 80% of predicted value in children participating to the present study (who did not receive inhaled steroids until one month before enrolment). The higher baseline levels in FEV<sub>1</sub>, with little room for improvement, may, therefore, contribute to explain the lack of effect on lung function for the group treated with montelukast in the study by Buchwald.<sup>22</sup> Similarly, the different therapeutic regimens may in part explain the different changes in FE<sub>NO</sub> levels observed in the two studies. In fact, in the present study, the FE<sub>NO</sub> levels at baseline were

not influenced by previous treatment with ICS and, therefore, it was possible to show more evident changes during the study periods, with no floor effect.

Since FE<sub>NO</sub>, but not FEV<sub>1</sub>, can reflect airway inflammation, an overall evaluation of the changes in the investigated parameters during this study allow to speculate that add-on therapy with montelukast, but not formoterol, is able to exert an adjunctive anti-inflammatory effect to low and medium dose budesonide in asthmatic children. In addition, the results of this study show that no difference in the investigated parameters could be observed between the two dosages of budesonide, therefore inducing to support the choice of an add-on therapy rather than an increase in the daily regimen of inhaled steroid in children not well controlled with low doses of budesonide.

In conclusion, this study has demonstrated that add-on therapy with montelukast to low dosage of budesonide is more effective than the addition of LABA or doubling the dose of budesonide in controlling airway inflammation measured as FE<sub>NO</sub> in asthmatic children.

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*Disclaimer.* Conflict of Interest Statement.

The authors declare they have no financial relationships or any other conflicts of interest that could inappropriately influence our actions regarding the subject matter or material discussed in the submitted manuscript.

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