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The effect of montelukast on respiratory symptoms and lung function in wheezy infants

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ABSTRACT: Our aim was to investigate the effectiveness of montelukast in recurrently wheezy infants.

We randomised 113, 6–24-month-old children with recurrent wheezing to receive either placebo or montelukast daily for an 8-week period. The primary end-point was symptom-free days. The secondary aims were to evaluate the effect of montelukast on rescue medication, on lung function, airway responsiveness and exhaled nitric oxide fraction (F_{ENO}). Clinical response and F_{ENO} were determined, the functional residual capacity (FRC) and specific airway conductance (sG_{aw}) were measured using an infant whole-body plethysmograph, the maximal flow at functional residual capacity ($V'_{max,FRC}$) was recorded using the squeeze technique and airway responsiveness was evaluated by performing a dosimetric methacholine challenge test.

There was no significant difference in changes in weekly symptom-free days between the montelukast and the placebo group (3.1–3.7 days *versus* 2.7–3.1 days, p=0.965). No significant differences were detected in the secondary end-points, *i.e.* use of rescue medication, FRC, sG_{aw}, $V'_{max,FRC}$, F_{ENO} or airway responsiveness between groups.

Montelukast therapy did not influence the number of symptom-free days, use of rescue medication, lung function, airway responsiveness or airway inflammation in recurrently wheezy, very young children.

KEYWORDS: Exhaled nitric oxide, infant, lung function, montelukast, treatment, wheeze

Inhaled corticosteroids (ICS) are the preferred long-term control medication in the treatment of pre-school children with recurrent wheeze. Leukotriene-receptor antagonists (LTRA) have been proposed as an alternative therapy for all age groups [1, 2]. The LTRA montelukast has been claimed to achieve improvements in asthma control outcomes [3–5], lung function, airway responsiveness [3, 6, 7] and exhaled nitric oxide fraction (F_{ENO}) [8] when used as monotherapy in children as young as 2 yrs of age. Although many trials have demonstrated that montelukast is beneficial and well tolerated in older children, few trials have been conducted in infants and very young children with wheeze. Treatment with montelukast is known to be a safe therapeutic option for infants with asthmatic symptoms [9, 10], but in only one study has montelukast revealed any positive effect on lung function, airway inflammation and asthma control. That study was conducted in a small, selected subgroup of wheezy infants [11].

The use of episodic and multiple-trigger wheezing phenotypes based on symptom-pattern has been recommended in pre-school wheezing disorders [12]. Children with episodic (viral) wheeze are not incapacitated between episodes whereas children with a multiple-trigger phenotype are also symptomatic between discrete exacerbations. The present study was designed to evaluate the efficacy of montelukast on numbers of symptom-free days in very young, recurrently wheezy children. The secondary aim was to evaluate the effect of montelukast on lung function, airway responsiveness, F_{ENO} and use of rescue medication. The hypothesis being tested was that montelukast would represent an effective treatment in these patients.

METHODS

The study was approved by the Ethics Committee of the Helsinki University Central Hospital (Helsinki, Finland). Written informed consent was obtained from the children's parents.

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Between September 2004 and April 2008, children born at full term and aged 6–24 months with troublesome dyspnoea and wheeze, with at least one wheezing episode being physician-diagnosed, and a successfully performed methacholine challenge test were included (fig. 1). Patients meeting all of the inclusion criteria were followed for 1–2 weeks, during which time parents completed diary cards twice daily. Children received as-needed inhaled terbutaline (0.25 mg per dose) *via* a steel spacer (Nebuchamber®; AstraZeneca, Lund, Sweden) to ease their respiratory symptoms. Subsequently, the children were randomly assigned to receive either montelukast (4 mg as an oral granule formulation) or placebo once in the evening for 8 weeks. The drug and the Nebuchambers were supplied by the pharmacy of Helsinki University Hospital (Helsinki, Finland). Patients were randomised to treatment in balanced blocks of four. The placebos were identical to the active drugs in terms of appearance and taste and were donated by the makers of the active agents. Patients were withdrawn from the study if they required steroid treatment.

The primary efficacy outcome was the number of symptom-free days. During the run-in and treatment periods, parents kept daily record cards of their child's respiratory symptoms, recording separately the day- and night-time scores together for wheeze, dyspnoea or shortness of breath using a visual analogue scale (VAS), ranging from 0 for no symptoms to 10 for the most severe symptoms. A symptom-free day was defined as a VAS score $\leqslant 0.5$ for day- and night-time and no use of rescue medicine. The parents were trained to record the symptoms by an experienced asthma nurse at a guidance session during the first visit. The secondary efficacy end-points were lung function, airway responsiveness, F_{ENO}, use of rescue medication and number of exacerbations. Atopy was defined by a positive skin-prick test (SPT) to food or aeroallergens.

Lung function was measured using commercial equipment (Babybody Masterscreen; Jaeger GmbH, Wurtzburg, Germany) according to a previously described protocol [13]. The functional residual capacity (FRC) and specific airway conductance (sG_{aw}) were measured using an infant whole-body plethysmograph [13–15]. Thereafter, the maximal flow at functional residual capacity ($V'_{max,FRC}$) was recorded using the squeeze technique reported elsewhere [13, 16]. F_{ENO} was assessed with a modification of the online single-breath measurement [17] described in detail in the online supplementary material. The dosimetric methacholine challenge test was performed as described in detail previously [13]. The provocative dose of methacholine causing a 40% fall in $V'_{max,FRC}$ (PD_{40} $V'_{max,FRC}$) was determined.

The study was designed to detect differences between the treatment groups, based on the primary end-point, *i.e.* the

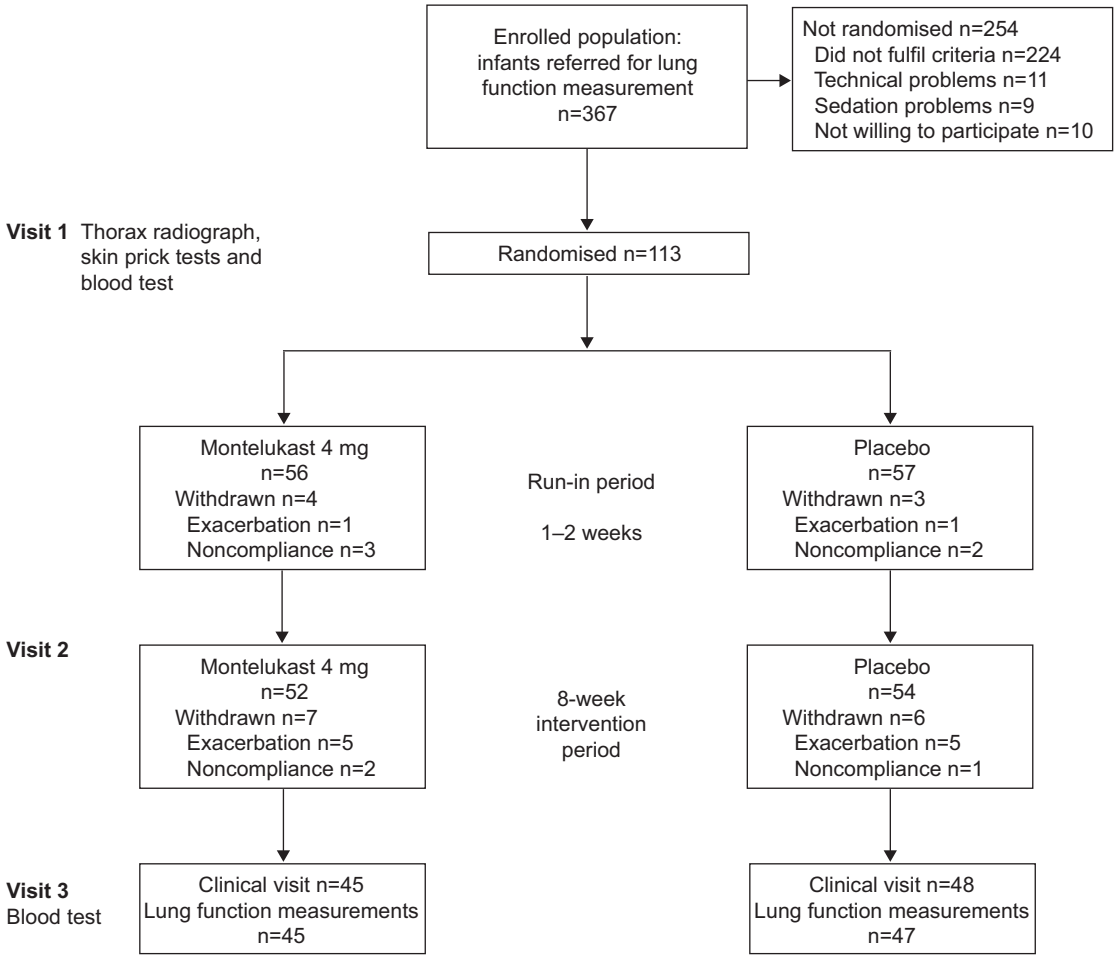

FIGURE 1. Flow chart showing patients' transition through the study.

proportion of symptom-free days at the end of treatment. A 5% significance level, one-way hypothesis and a power of 90% were used in calculating the sample size. We used the data of a previous study design in hospitalised infants with respiratory syncytial virus (RSV) bronchiolitis [18]. By anticipating a similar effect in the infants with wheeze, the present study was estimated to require 56 infants in both treatment arms in order to detect a statistically significant difference. All daily diary card variables were analysed as changes from baseline. Symptoms and rescue medication use in the last week of the run-in period and in the treatment weeks were analysed for each parameter. We chose the seventh treatment week as the end-point.

For categorical variables, Chi-squared test or Fisher's exact test were used, whereas Mann–Whitney's U-test or unpaired t-test were used for between treatment comparisons in lung function and inflammatory markers. The interaction between time and group in symptom-free days and the use of rescue medication was analysed using ANOVA with repeated measures. In the *post hoc* analysis, the relationships between changes in symptom-free days and use of rescue medications and atopic eczema, family history of asthma, SPT positivity, total eosinophil count or F_{eNO} values were examined by ANOVA with repeated measures. The data were analysed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients

A total of 113 infants and very young children fulfilling the inclusion criteria were randomised to the study.

In figure 1 the study flow diagram shows that a group of 254 children were not randomised. 56 patients were randomised to montelukast and 57 to placebo treatment and a total of 93 patients completed the study. Five randomised patients had to be withdrawn due to lack of parental compliance and two patients due to exacerbations experienced during the run-in period. The baseline demography for the 113 patients is shown in table 1.

Most subjects (74%) were males and the mean age at randomisation was 15 months. In our study group of children, 83% had dyspnoea and wheeze both during and between colds. During the run-in period, the children displayed symptoms on a median of 56% of days and the mean use of rescue medication was 3.6 days per week. The mean duration of respiratory symptoms in these patients was 8 months. All children experienced recurrent wheezing episodes, at least one of which was required to be physician diagnosed. 34% of the patients had a history of hospitalisation due to wheezing. The two treatment groups were well matched with respect to demographic and baseline data with the exception that the percentage with a family history of asthma tended to be higher in montelukast group ($p=0.091$).

Adherence to the study medication regimen was estimated based on returned medications. Study medications were used in a median of 98% (range 81–100%) of treatment periods during the trial and use did not differ between the two treatment groups.

Efficacy evaluations

During the run-in period, the mean number of symptom-free days and weekly use of rescue medication were 3.1 and 14.4 puffs in the montelukast, and 2.7 and 10.6 puffs in the placebo group, respectively. There were no significant differences in changes in symptom-free days between the montelukast and placebo groups in response to treatment: mean±SD changes for montelukast and placebo were 3.1±2.7 to 3.7±2.9 days and 2.7±2.5 to 3.1±3.0 days, respectively ($p=0.965$) (fig. 2a). Furthermore, there were no significant differences between the changes in the use of rescue medication between treatment groups (fig. 2b).

At baseline, the median FRC, sG_{aw} and $V'_{max,FRC}$ values were within the normal range in both groups and after the treatment, there were no significant between-group differences in the changes in these parameters. At baseline, median (interquartile range) PD_{40} $V'_{max,FRC}$ and F_{eNO} were 0.58 (0.3–0.9) mg and 15.6 (8.1–32.1) ppb in the montelukast group and 0.49 (0.2–1.1) mg and 19.4 (13.6–27.1) ppb in the placebo group, respectively. At baseline, F_{eNO} measurements were available for 89 children. After the treatment period, the methacoline challenge test was successfully performed in a total of 77 children and F_{eNO} measurements undertaken in 71 children. There were no significant differences in changes in these parameters between the groups (table 2).

Seven patients had to be withdrawn from the montelukast group and six from the placebo group during the 8-week treatment period (fig. 1 and table 3). 10 patients were withdrawn due to an exacerbation that required systemic treatment. There were no statistical significant differences between the groups with respect to these exacerbations. Two children

TABLE 1 Baseline characteristics of the study children

	Montelukast	Placebo
Subjects n	56	57
Age months	15.5±5.5	14.3±5.0
Male sex	42 (75)	42 (74)
Gestational age weeks	39.6±1.6	39.9±1.4
Birthweight g	3467±507	3682±454
Family history of asthma	33 (58.9)	24 (42.1)
Parental asthma	27 (48.2)	20 (35.1)
Maternal asthma	16 (28.6)	14 (24.6)
Atopic eczema	22 (39.3)	29 (50.9)
Skin-prick test positive	14 (25)	18 (32)
Parental smoking	14 (25.0)	22 (38.6)
Duration of symptoms months	8.2±4.5	7.2±3.8
History of physician diagnosed wheezing		
Total	56 (100)	57 (100)
1 episode of wheezing	12 (21.4)	15 (26.3)
2 episodes of wheezing	19 (33.9)	22 (38.6)
⩾3 episodes of wheezing	25 (44.6)	20 (35.1)
Hospital admission for wheezing	22 (39.3)	16 (28.1)
Symptom-free days days per week	3.1±2.7	2.7±2.5
Use of rescue medication days per week	3.8±2.9	3.5±2.7
Use of rescue medication puffs per week	14.4±15.4	10.6±13.1

Data are presented as mean±SD or n (%), unless otherwise stated.

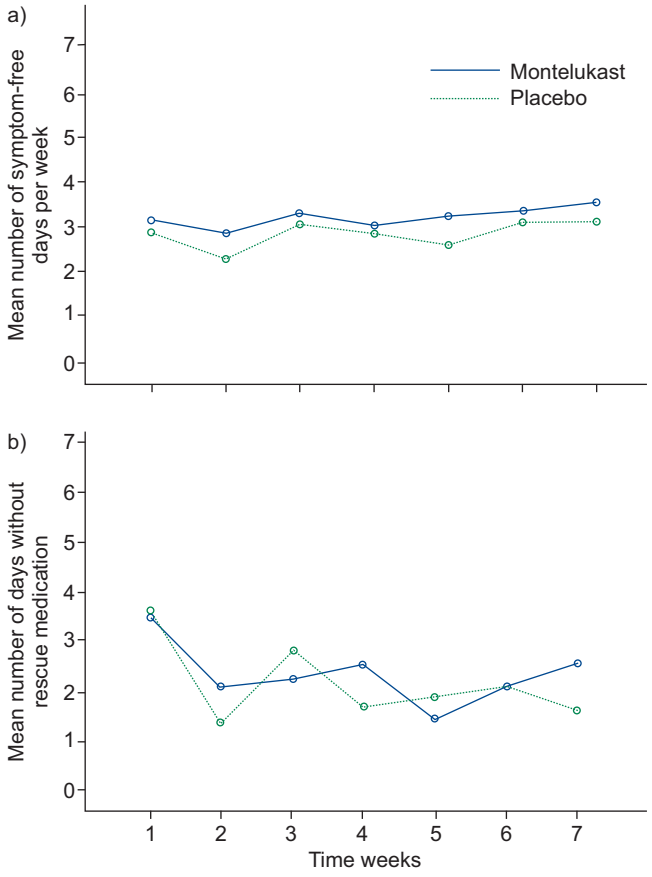

FIGURE 2. Weekly prevalence of a) symptom-free days and b) days without rescue medication. There were no statistical differences between groups.

were hospitalised because of dyspnoea in the montelukast group and four children in the placebo group. In the montelukast group and the placebo group, 17 and 20 children, respectively, needed the assistance of a physician due to their respiratory symptoms (table 3).

In the *post hoc* analysis, we tested the effectiveness of treatment on numbers of symptom-free days and use of rescue medication in patients with asthma predictive factors. The response to treatment was independent of the presence or absence of concurrent atopic eczema, family history of asthma, SPT positivity, total eosinophil count or F_{ENO}.

Safety

Safety and tolerability were assessed by clinical evaluation and adverse experience monitoring. An adverse experience included any unfavourable change or worsening in the patients during the treatment period. Montelukast treatment was generally well tolerated. There were no statistically significant differences in the proportion of clinical or drug-related adverse experiences in montelukast (82.4% and 9.6%, respectively) and placebo groups (86.8% and 3.7%, respectively) during treatment ($p=0.271$ and $p=0.380$, respectively). Tables S4 and S5 list drug-related and clinically adverse experiences during treatment. No patient in the montelukast group discontinued treatment because of an adverse event that was considered by the investigators to be drug-related.

DISCUSSION

This study investigated the effect of montelukast therapy on clinical signs and on objective parameters in recurrently wheezy children aged 6–24 months. The results demonstrated that 8 weeks of montelukast therapy had no effect on the number of symptom-free days, use of rescue medication, the number of exacerbations, lung function, airway responsiveness or on the extent of airway inflammation in these patients. The response to treatment was independent of the presence or absence of concurrent atopic eczema, family history of asthma or SPT positivity. On the positive side, montelukast treatment was well tolerated.

The pathophysiology of wheeze and the effectiveness of treatment changes with age. In placebo-controlled studies, montelukast has been reported to be safe and effective in school-aged children with persistent symptoms [3], as well as in pre-school children with persistent [4] or intermittent symptoms [5]. LTRAs block the action of cysteinyl leukotrienes, which catalyse the inflammatory cascade emerging from eosinophils, mast cells and alveolar macrophages [19]. Montelukast improves lung function and reduces bronchoconstriction induced by exercise, cold air and methacholine in school-aged [3, 20] and in pre-school children [6, 7]. In addition, in school-aged asthmatic children, montelukast has been found to improve inflammatory biomarkers [21]. However, when compared with low-dose ICS treatment, it has consistently been less effective in children aged >2 yrs [22]. The excellent safety profile, oral administration route, once-daily dosing and, possibly, better adherence to treatment are the advantages of montelukast. Due to its safety and the ease of oral administration, montelukast may seem like an attractive drug in the treatment of very young children.

We tested the hypothesis that montelukast would represent effective treatment in very young recurrently wheezy children. Before treatment, 83% of our patients experienced dyspnoea or wheeze both during and between colds, and they could be phenotyped as multiple-trigger wheezers. The rest suffered troublesome viral wheeze. Children had used rescue medication on average on >3 days per week. The mean duration of respiratory symptoms of the recruited patients was ~8 months. It has to be emphasised that the children in our study represent a subgroup of the vast number of young wheezy children. Our hospital is a tertiary centre and the children evaluated probably represent the more severe end of the spectrum.

The National Asthma Education and Prevention Program recommends that a physician should consider daily controller medication trial for children who consistently require symptomatic treatment >2 days per week for >4 weeks [1]. According to the National Asthma Education and Prevention Program, the ranking of evidence of the expert panel was D, *i.e.* panel consensus judgement without clinical literature addressing the subject. The preferred treatment is daily ICS at a low dose with alternative treatments including montelukast [1]. Recently, the PRACTALL (PRACTical ALLergy) guidelines for paediatric asthma have also proposed that montelukast may be used occasionally even as a first line treatment in wheezy infants [2]. However, there is very little evidence to back up these recommendations. Maintenance treatment with ICS is recommended in European Respiratory Society Task Force recommendations for multiple-trigger

TABLE 2 Lung function, airway responsiveness, exhaled nitric oxide, total immunoglobulin (Ig)E and blood eosinophils before and after 8 weeks' treatment with either montelukast or placebo

	Montelukast		Placebo		p-value#
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	
Subjects n	56	45	57	47	
FRC mL	253 (205–275)	263 (235–304)	231 (197–279)	264 (228–324)	0.260
FRC z-scores	0.90 (-0.1–2.1)	1.20 (0.3–2.3)	0.15 (-0.7–1.4)+	0.85 (-0.1–2.0)	0.824
sGaw $kPa^{-1}\cdot s^{-1}$	1.8 (1.0–3.4)	2.5 (1.2–3.9)	1.9 (1.2–3.3)	1.7 (1.2–3.5)	0.277
sGaw z-scores	-1.7 (-3.6–2.6)	0.1 (-2.9–3.9)	-1.2 (-3.3–2.1)	-1.90 (-2.9–2.6)	0.287
$V'_{max,FRC}$ $mL\cdot s^{-1}$	211 (145–290)	279 (178–374)	185 (144–271)	228 (176–317)	0.364
$V'_{max,FRC}$ z-score	-1.1 (-1.8– -0.3)	-0.5 (-1.5–0.6)	-1.1 (-2.1– -0.6)	-0.9 (-1.8–0.2)	0.941
PD_{40} $V'_{max,FRC}$ mg	0.58 (0.3–0.9)	0.49 (0.2–1.1)	0.43 (0.2–1.2)	0.51 (0.2–1.1)	0.513
F_{ENO} ppb¶	15.6 (8.1–32.1)	19.4 (13.6–27.1)	21.3 (15.7–32.7)	19.6 (11.6–27.9)	0.452
Total IgE $kU\cdot L^{-1}$	22 (9–68)	31 (11–54)	17.5 (9–67)	25 (8–84)	0.128
Total eosinophils $\times 10^9$ $cells\cdot L^{-1}$	0.29 (0.16–0.48)	0.25 (0.17–0.38)	0.21 (0.13–0.38)	0.25 (0.15–0.42)	0.133

Data are presented as median (interquartile range), unless otherwise stated. FRC: functional residual capacity; sGaw: specific airway conductance; $V'_{max,FRC}$: maximal expiratory flow at FRC; PD_{40} $V'_{max,FRC}$: provocative dose of methacoline causing a 40% fall in forced expiratory flow at FRC; F_{ENO}: exhaled nitric oxide fraction. #: t-test was applied in all other comparisons except in F_{ENO} analysis where Mann-Whitney U-test was used; ¶: at baseline, F_{ENO} measurements were available in 89 children and after the treatment period in 71 children; +: p=0.007 *versus* placebo and montelukast at baseline.

wheeze and ICS or montelukast on a trial basis in small children with recurrent wheeze [12]. According to a recent meta-analysis, infants and pre-schoolers, with recurrent wheezing suffered fewer symptoms and improved their lung function during ICS treatment [23]. Our results do not fully support the current recommendations in the international asthma guidelines. There are clearly too few trials available that have evaluated the effectiveness of montelukast treatment in very young children with recurrent wheeze.

Our study's negative results are consistent with the report of VAN ADELSBERG *et al.* [9], where very young children aged 6–24 months with physician-diagnosed asthma or at least three ''asthma-like'' episodes were treated with montelukast or placebo for a 6-week period. One-half of the patients were already being treated with ICS. That study was primarily intended to evaluate safety. There were no differences in adverse effects in study groups. There were no significant differences between the treatment groups in reduction in asthma symptoms in the measures of efficacy that were the secondary outcomes of this trial. However, in contrast to our findings, in a *post hoc* analysis, it did seem that there were significantly fewer days with rescue medication in the montelukast group compared with the placebo group in patients with a history of allergic rhinitis or atopic dermatitis or among those children whose parents were asthmatics. Similarly, a recent study reported a beneficial effect of 4 weeks of montelukast treatment on lung function, airway inflammation and symptom scores in children aged 10–26 months in a well-defined subgroup of wheezy infants. These children had a history of recurrent wheeze, proven allergy, elevated F_{ENO} (>15 ppb) and a positive family history of asthma [11].

TABLE 3 Number of wheezing exacerbations during treatment period

	Montelukast	Placebo
Subjects	52	54
Exacerbation episodes at home#	60	65
Healthcare resource use because of wheeze	17	20
Adding of home rescue medication	4	6
Oral corticosteroid	3	1
Bronchodilating medication	10	13
Hospital admission because of wheeze	2	4

Data are presented as n. #: any three consecutive days and/or nights with symptoms and at least two treatments with inhaled terbutaline per day.

One limitation of our study is the heterogeneity of the patients and, thus, some possibly unseen beneficial effect of montelukast in some subgroups. 83% of our children with recurrent wheeze were multiple-trigger and 17% viral wheezers, and we did not select them based on either atopy or family history. In the study of STRAUB *et al.* [11], wheezing infants were included only if they had signs of allergy and a positive family history of asthma. Thus, genetic heterogeneity and different wheezing phenotypes may explain the variable response of infants to montelukast [12]. Several studies have demonstrated an increased risk for persistent asthma in young children with frequent wheezing during the first 3 yrs of life who have a parental history of asthma, eczema or allergic rhinitis [24]. If one were to use these features as inclusion criteria then it could be possible to achieve a degree of homogeneity with regard to phenotype and maximise the likelihood of a positive response to anti-inflammatory treatment. Earlier data also imply that atopic, wheezy, very young children are more likely to respond to ICS therapy than their nonatopic counterparts [25].

However, in a recent meta-analysis, the beneficial effects of ICS were found to be independent of atopic condition [23]. In the subgroup analysis of our montelukast study, the response to treatment was also independent of atopic status. It is important to note that children in this youngest age group may be too young to have completely manifested atopy.

Our primary measure of efficacy was symptom-free days. In addition, we evaluated the effect of montelukast on the use of rescue medication and on objective parameters, such as baseline lung function, airway responsiveness and F_{ENO}, as a marker of inflammation, all with negative results. Although lung function measurements may correlate poorly with symptoms as scored by parents of wheezing infants, in our earlier study, which was conducted in recurrently symptomatic infants, increased airway responsiveness was associated with reduced baseline lung function, a history of physician-confirmed wheeze and atopic characteristics [13]. There is some evidence that reduced lung function and increased airway responsiveness are predictive of the development of asthma at a later age. We have shown recently that reduced lung function in infancy was associated with respiratory morbidity and treatment need at the age of 3 yrs [26]. Thus, in infants with wheeze, the evaluation of treatment efficacy should preferably include also these objective end-points. There are few studies conducted in infants that have measured objective data on lung function to date. We have also shown previously that inhaled budesonide can improve sG_{aw} in infants with reduced lung function and recurrent respiratory symptoms [25]. In contrast, it is still unclear whether airway responsiveness can be modified by any treatment at this age.

Testing of respiratory function in infants requires expertise and we acknowledge that each technique used in the current study has potential limitations, sources of error and inherent variability that may confound the results. However, lung function was assessed according to standardised protocols using the plethysmographic and rapid thoracoabdominal compression techniques [27, 28], and a previously validated method was used to measure airway responsiveness [13]. Even in the measurement of F_{ENO}, efforts were made to standardise flow during sampling of exhaled air by using a modified single breath technique; nonetheless, the results in the current study may have been confounded by ambient and upper airway nitric oxide [29].

The power calculation used in our study was based on the RSV bronchiolitis study [18]. It is possible that power was based on an unrealistically large treatment effect meaning that too few patients were recruited, which may partly explain the negative results. Infants with asthmatic symptoms may have fewer symptoms compared with children with a recent history of RSV bronchiolitis. However, in the study of young children with asthma (age range 12–47 months) by BISGAARD *et al.* [30], during the run-in period, the children had symptoms on a median of 81% days compared with 100% of children in the RSV bronchiolitis study [18].

In the asthma study by BISGAARD *et al.* [30], it was impossible to determine exact treatment results concerning symptom-free days although higher dose of ICS significantly increased symptom-free days as compared with placebo. In addition, our treatment period was rather a short-term intervention. However, in the study of STRAUB *et al.* [11], a 4-week period of montelukast was capable of alleviating symptoms, as well as F_{ENO}, and improved lung function. Our study was also not intended to reveal the long-term benefit of montelukast therapy, *e.g.* the possibility that montelukast could reduce exacerbations. This question, as well as the value of montelukast as an add-on therapy, and its benefits in special subgroups in this age group, need further clarification.

In conclusion, 8 weeks of montelukast therapy had no effect on the number of symptom-free days, use of rescue medication, lung function or on airway responsiveness in recurrently wheezy, very young children. The response to treatment was independent of risk factors for future asthma. These findings are in concordance with previous studies highlighting the poor efficacy of anti-inflammatory drugs in reducing asthmatic symptoms in wheezy, very young children. Further studies in this patient group will be required to identify a safe and effective therapy for these infants.

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CLINICAL TRIAL

The study is registered at www.clinicaltrials.gov with identifier NCT00934713.

STATEMENT OF INTEREST

Statements of interest for A.S. Pelkonen, L.P. Malmberg and M.J. Mäkelä, and for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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