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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 randomized 113, 6 to 24 month old children with recurrent wheezing to placebo or montelukast daily for a 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 (AR) and exhaled nitric oxide (FE_{NO}). Clinical response and FE_{NO} were determined, the functional residual capacity (FRC) and specific airway conductance (sGaw) 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 AR was evaluated by performing a dosimetric methacholine challenge test.

There was no significant difference in changes towards weekly symptom-free days between the montelukast and the placebo group (3.1 to 3.7 days vs 2.7 to 3.1 days, p=0.965). No significant differences were detected in the secondary end points, i.e. use of rescue medication, in FRC, sGaw, $V´max_{FRC}$ or FE_{NO} values or AR between groups.

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

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

INTRODUCTION

Inhaled corticosteroids (ICS) are the preferred long-term control medication in the treatment of preschool 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], in lung function and airway responsiveness (AR) [3, 6, 7] and in the exhaled nitric oxide level (FE_{NO}) [8] when used as monotherapy in children as young as 2 years 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 preschool wheezing disorders[12]. Children with episodic (viral) wheeze are not incapacitated between episodes whereas children with multiple-trigger phenotype are symptomatic also between discrete exacerbations. The present study was designed to evaluate the efficacy of montelukast on numbers of symptom-free days in very young, recurrently wheeze children. The secondary aim was to evaluate the effect of montelukast on lung function, AR, FE_{NO} 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. Written informed consent was obtained from the childrens´ parents. Between September 2004 and April 2008, full-term children, aged 6 to 24 months, with troublesome dyspnea 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 to 2 weeks, during which parents completed diary cards twice daily. Children received as needed inhaled terbutaline 0.25 mg/dose via the steel spacer, Nebuchamber®, (manufactured by AstraZeneca, Lund, Sweden) to easy their respiratory symptoms. Subsequently, the children were randomly assigned to receive either montelukast 4 mg as an oral granule formation or placebo once in the evening for 8 weeks. The drug and the nebuchambers were supplied by the pharmacy of Helsinki University Hospital. Patients were randomized to treatment in balanced blocks of four. The placebos were identical to active drugs in terms of appearance and taste and were also 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 daytime and night-time scores together for wheeze, dyspnea, or shortness of breath using a Visual Analog Scale, ranging from 0 for no symptoms to 10 for the most severe symptoms. Symptom free days was defined as a VAS score ≤ 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 endpoints were lung func-

tion, AR, $FE_{NO,}$ use of rescue medication and the number of exacerbations. Atopy was defined by a positive skin-prick test (SPT) to food or aeroallergens.

The lung function was measured using commercial equipment (Babybody Master-screen; Jaeger GmbH, Wurtzburg, Germany) according to an earlier described proto-col [13]. The functional residual capacity (FRC) and specific airway conductance (sGaw) were measured using an infant whole-body plethysmograph [13-15]. Thereaf-ter, the maximal flow at functional residual capacity ($V'max_{FRC}$) was recorded using the squeeze technique reported elsewhere [13, 16]. The fraction of FE_{NO} was assessed with a modification of the online single-breath measurement [17] described in detail in the online depository. 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 endpoint i.e. the proportion (%) of symptom-free days at the end of treatment. A 5% significance level, one-way hypothesis and a power of 90% was used in calculating the sample size. We used the data of a previous study design in hospital-ized 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 analyzed 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 where-as Mann-Whitney´s U-test or 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 analyzed 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 excema, family history of asthma, SPT positivity, total eosinophil count or FE_{NO} values were examined by ANOVA with repeated measures. The data were analyzed using SPSS for Windows software version 17.0 (Inc, Chicago, IL).

RESULTS

Patients

A total of 113 infants and very young children fulfilling the inclusion criteria were randomized to the study. With respect to the group of 254 children not randomized see figure 1. Fifty-six patients were randomised to montelukast and 57 to placebo treatment and a total of 93 patients completed the study. Five randomized patients had to be withdrawn due to lack of parental compliance and 2 patients due to exacerbations experienced during the run-in period. The study flow diagram is shown in figure 1. The baseline demography for the 113 patients is shown in table 1.

Most (74 %) were boys and the mean age at randomization was 15 months. In our study group of children, 83% had dyspnea and wheeze with 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. Thirty-four % of the patients had a history of hospitalization 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 98 %, (median, range 81-100 %) of treatment periods during the trial and use did not differ in 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 montelukast, and 2.7 and 10.6 puffs in placebo groups, respectively. There were no significant differences in changes in symptom-free days between 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) and 2.7 (2.5) to 3.1 (3.0) days, respectively (p=0.965) (fig. 2a). Futhermore, there were no significant differences in the changes in the use of rescue medication between treatment groups (fig. 2b).

At baseline, the median FRC, sGaw 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 FE_{NO} were 0.58 (0.3-0.9) mg and 15.6 (8.1-32.1) ppb in montelukast group and 0.49 (0.2-1.1) mg and 19.4 (13.6-27.1) ppb in placebo group, respectively. At baseline, FE_{NO} measurements were available for 89 children. After the treatment period, the methacoline challenge test was successfully performed in a total of 77 children and FE_{NO} 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 6 from the placebo group during the eight week treatment period (fig. 1, table 3). Ten patients were withdrawn due to an exacerbation which required systemic treatment. There were no statistical significant differences between the groups with respect to these exacerbations. Two children were hospitalized because of dyspnoea in the montelukast group and 4 children in the placebo group. In the two groups, 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 level of FE_{NO}.

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% and placebo groups 86.8% and 3.7% during treatment, p=0.271 and p=0.380 respectively. Tables 4 and 5 list drug-related and clinical adverse experiences during treatment and can be found in the online depository. No patient in the montelukast group discontinued treatment because of an adverse event which 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 to 24 months. The results demonstrated that 8 weeks´ montelukast therapy had no effect on the number of symptom-free days, use of rescue medication, the number of exacerbations, lung function, AR 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 preschool children with persistent [4] or intermittent symptoms [5]. LTRAs block the action of cysteinyl leukotrienes, which catalyze 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 preschool 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 years [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% our patients experi-

enced dyspnea 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 more than three days per week. The mean duration of respiratory symptoms of the recruited patients was about eight months. It has to be emphasized 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 likely represent the more severe end of the spectrum.

The National Asthma Education and Prevention Program (NAEPP) recommends that a physician should consider daily controller medication trial for children who consistently require symptomatic treatment >2 days a week for > 4 weeks [1]. 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 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 ERS Task Force recommendations for multiple-trigger wheeze and ICS or montelukast on a trial basis in small children with recurrent wheeze [12]. According to a recent meta-analysis, infants and preschoolers, with recurrent wheezing suffered less 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 which 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 six to 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 ICSs. 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 which 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 monte-lukast group compared to placebo 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 to 26 months in a well-defined subgroup of wheezy infants. These children had a history of recurrent wheeze, proven allergy, elevated FE_{NO} (>15 ppb) and a positive family history of asthma [11].

One limitation of our study is the heterogeneity of the patients and thus, some pos-sible unseen beneficial effect of montelukast in some sub-group. Of our children with recurrent wheeze, 83% 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 years 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, AR and FE_{NO} 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 AR 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 AR 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 years [26]. Thus, in infants with wheeze, the evaluation of treatment efficacy should preferably include also these objective endpoints. There are few studies conducted in infants which have measured objective data on lung function to date. We have also shown previously that inhaled budesonide can improve sGaw in infants with reduced lung function and recurrent respiratory symptoms [25]. In contrast, it is still unclear whether AR 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 which may confound the results. However, lung function was as-

sessed according to standardized protocols using the plethysmographic and rapid thoracoabdominal compression techniques [27, 28] and a previously validated method was used to measure AR [13]. Even in the measurement of $FE_{NO,}$ efforts were made to standardize 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 NO [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 unrealistic 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 to children with a recent history of RSV bronchiolitis. However, in Bisgaard´s study of young children with asthma (age range 12 to 47 months), 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, 30]. In this asthma study, 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 four week period of montelukast was capable of alleviating symptoms as well as FE_{NO} 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 as well as its benefits in special subgroups in this age group, needs further clarification.

In conclusion, eight weeks of montelukast therapy had no effect on the number of symptom-free days, use of rescue medication, lung function or on airway responsive-

ness in recurrent 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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TABLE 1: Baseline characteristics of the study children*

	Montelukast	Placebo
Number of subjects	56	57
Age months	15.5 ± 5.5	14.3 ± 5.0
Male sex, no. (%)	42 (75)	42 (74)
Gestational age weeks	39.6 ± 1.6	39.9 ± 1.4
Birth weight g	3467 ± 507	3682 ± 454
Family history of asthma, no (%)	33 (58.9)	24 (42.1)
Parental asthma, no (%)	27 (48.2)	20 (35.1)
Maternal asthma, no (%)	16 (28.6)	14 (24.6)
Atopic eczema, no (%)	22 (39.3)	29 (50.9)
Skin-prick test positive, no (%)	14 (25)	18 (32)
Parental smoking, no (%)	14 (25.0)	22 (38.6)
Duration of symptoms, months	8.2 ± 4.5	7.2 ± 3.8
History of physician diagnosed wheezing, no (%)	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 / wk)	3.1 ± 2.7	2.7 ± 2.5
Use of rescue medication (days / wk)	3.8 ± 2.9	3.5 ± 2.7
Use of rescue medication (puffs / wk)	14.4 ± 15.4	10.6 ± 13.1

* Plus-minus values are means ± SD.

TABLE 2: Lung function, airway responsiveness, exhaled nitric oxide, total IgE and blood eosinophils before and after 8 weeks´ treatment with montelukast or placebo

	Montelukast		Placebo		
	Pre	Post	Pre	Post	p-value[1]
Number of subjects	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 $kPa^{-1}s^{-1}$	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 mls^{-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
FENO 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/L	22 9 – 68	31 11 – 54	17.5 9 – 67	25 8 - 84	0.128
Eos abs 10E9/L	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

Definition of abbreviations: FRC = functional residual capacity, sGaw = specific airway conductance, V´max, FRC = maximal expiratory flow at functional residual capacity, PD_{40}V´max,FRC = provocative dose of methacoline causing a 40% fall in forced expiratory flow at functional residual capacity, FENO = nitric oxide in exhaled air, IgE = immunoglobulin E, abs eos = total eosinophils, ECP = eosinophilic cationic protein. Data are presented as median (interquartile range). *p=0.007 vs placebo and montelukast at baseline. ¤At baseline, FE_{NO} measurements were available in 89 children and after the treatment period in 71 children. [1)] T-test was applied in all other comparisons except in FENO analysis where Mann-Whitney`s U-test was used.

TABLE 3: Number of wheezing exacerbations during treatment period

	Montelukast N = 52	Placebo N = 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

* Any three consecutive days and/or nights with symptoms and at least two treatments with inhaled terbutaline per day.

Figure 1. Patient flow through the study

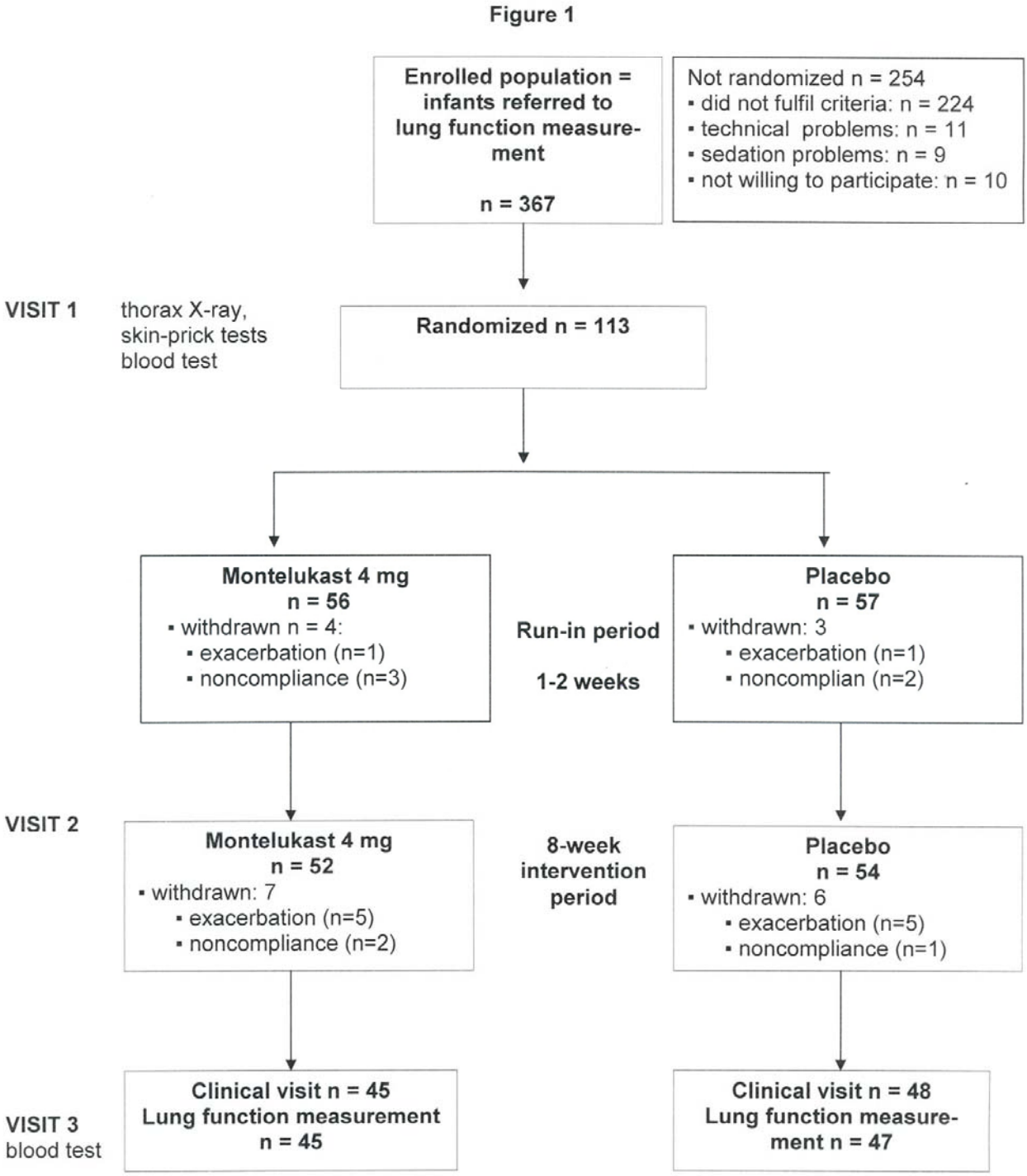
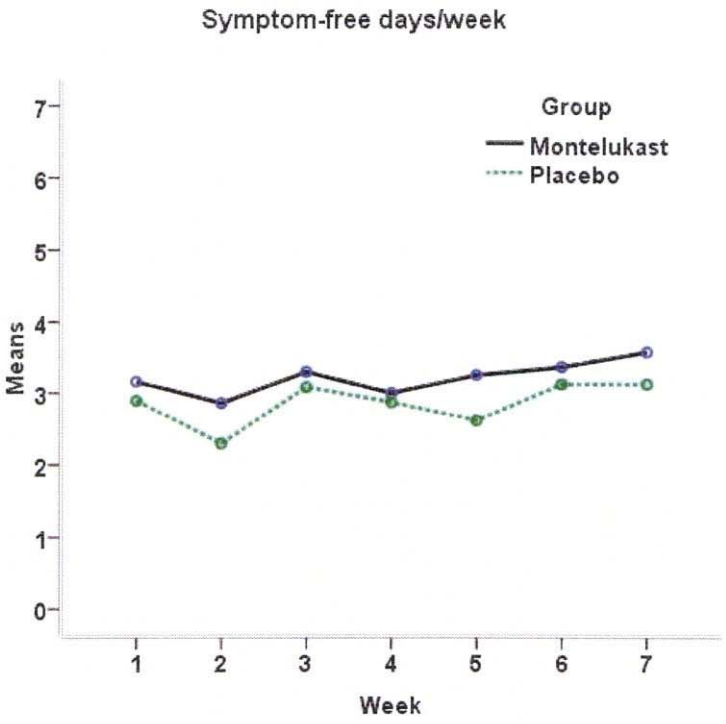


Figure 2 a. Prevalence of weekly symptom-free days. There were no statistical differences between groups.

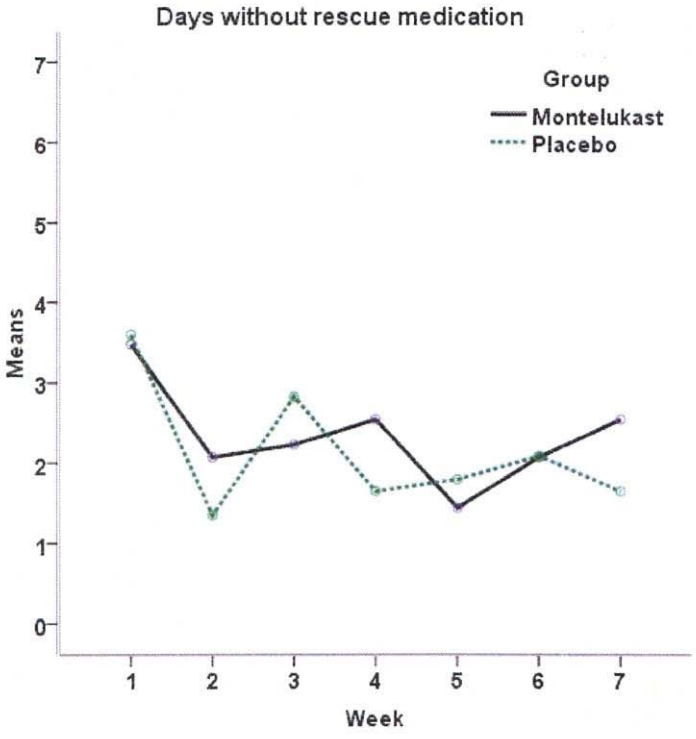
Figure 2 b. Weekly prevalence of days without rescue medication. There were no statistical differences between groups.

Figure 2

a


Symptom-free days/week
Group
Montelukast
Placebo
Means
0
1
2
3
4
5
6
7
1
2
3
4
5
6
7
Week

b


Days without rescue medication
Group
Montelukast
Placebo
Means
0
1
2
3
4
5
6
7
1
2
3
4
5
6
7
Week