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A Double-Blind, Placebo-Controlled, Randomized Trial of Montelukast for Acute Bronchiolitis

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What's Known on This Subject

Bronchiolitis is a major health burden with no proven specific therapy. Whereas CysLTs are implicated in the inflammation of bronchiolitis, we hypothesized that a specific CysLT receptor antagonist, montelukast, would improve the clinical course and cytokines' response in acute bronchiolitis.

What This Study Adds

A placebo-controlled, double-blind, randomized trial was conducted in 53 infants with acute bronchiolitis. Montelukast had no effect on hospital LOS, clinical course, or cytokines' response when given in the early acute phase.

ABSTRACT

BACKGROUND. Cysteinyl leukotrienes are implicated in the inflammation of bronchiolitis. Recently, a specific cysteinyl leukotriene receptor antagonist, montelukast (Singulair [MSD, Haarlem, Netherlands]), has been approved for infants in granule sachets.

OBJECTIVE. Our goal was to evaluate the effect of montelukast on clinical progress and on cytokines in acute bronchiolitis.

METHODS. This was a randomized, placebo-controlled, double-blind, parallel-group study in 2 medical centers. Fifty-three infants (mean age: 3.8 ± 3.5 months) with a first episode of acute bronchiolitis were randomly assigned to receive either 4-mg montelukast sachets or placebo, every day, from hospital admission until discharge. The primary outcome was length of stay, and secondary outcomes included clinical severity score (maximum of 12) and changes in type 1 and 2 cytokine levels (including interleukin4/IFN- γ ratio as a surrogate for the T-helper 2/T-helper 1 ratio) in nasal lavage.

RESULTS. Both groups were comparable at baseline, and cytokine levels correlated positively with disease severity. There were neither differences in length of stay (4.63 ± 1.88 [placebo group] vs 4.65 ± 1.97 days [montelukast group]) nor in clinical severity score and cytokine levels between the 2 groups. No differences in interleukin 4/IFN- γ ratio between the 2 groups were seen. There was a slight tendency for infants in the montelukast group to recover more slowly than those in the placebo group (clinical severity score at discharge: 6.1 ± 2.4 vs 4.8 ± 2.2 , respectively).

CONCLUSIONS. Montelukast did not improve the clinical course in acute bronchiolitis. No significant effect of montelukast on the T-helper 2/T-helper 1 cytokine ratio when given in the early acute phase could be demonstrated. *Pediatrics* 2008;122:e1249–e1255

BRONCHIOLITIS IS THE most common infantile respiratory illness resulting in hospital admission and is associated with considerable morbidity.^{1,2} Bronchiolitis is commonly followed by recurrent wheeze and other asthma-like symptoms.^{2–5} Effective evidence-based therapy for bronchiolitis is unknown. The usefulness of bronchodilators is controversial,⁶ and the limited evidence available does not support the routine use of steroid therapy.^{7–11} The use of hypertonic saline inhalation needs more systematic study.¹² Thus, new treatments are required.

Inflammatory mechanisms in bronchiolitis have been documented recently, including increased airway secretion, mucosal edema, and infiltration of inflammatory cells.¹³ Cysteinyl leukotrienes (CysLTs) are released during respiratory syncytial virus (RSV) airway infection in infants, and their levels

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Drs Amirav, Luder, and Mandelberg conceived the study and prepared the protocol, planned the statistical analysis, and provided intellectual input to study design; Drs Amirav, Luder, Mandelberg, Kruger, Borovitch, Babai, and Tal supervised acquisition of study data; and Drs Miron, Babai, Tal, and Zuker were responsible for virology and cytokine studies. All authors contributed to the interpretation of study results and critically reviewed the manuscript. Dr Amirav had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00524693).

Key Words

bronchiolitis, controlled clinical trial, pediatrics, montelukast, respiratory syncytial virus

Abbreviations

CysLT—cysteinyl leukotriene
LOS—length of stay
RSV—respiratory syncytial virus
Th—T helper
IL—interleukin
IFN—interferon
CS—clinical score
AR—adverse reaction

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are significantly elevated.^{14–18} CysLTs are known to cause bronchial obstruction, mucosal edema, and infiltration of eosinophilic granulocytes and to increase bronchial responsiveness.¹⁹ In addition, RSV bronchiolitis is associated with a profound imbalance in cytokine species, with deficient type 1 and excessive type 2 responses.²⁰ This imbalance may be a contributing factor toward the future development of asthma.

Recently specific CysLT receptor antagonists such as montelukast (Singular [MSD, Haarlem, Netherlands]) have become available for use in children,¹⁹ with a granule formulation designed for toddlers. Montelukast has recently been shown to modify a typical T-helper 2 (Th2) cytokine pattern (interleukin 4 [IL-4] and IL-13) toward Th1 (interferon γ [IFN- γ]) predominance in children with asthma.²¹ Montelukast was shown to reduce asthma-like exacerbations when treatment was started 7 days after the first symptoms of bronchiolitis.²² Moreover, montelukast was recently shown effective when started early in acute (mostly viral-induced) asthma/wheezing in young children and infants.^{23,24} No study has evaluated the effect of early (day 1 of admission) intervention with montelukast in infants hospitalized with acute bronchiolitis. If montelukast can alter this initial Th2/Th1 imbalance in acute bronchiolitis, it may have significant implications for both bronchiolitis and asthma. The objective of the present randomized, double-blind, placebo-controlled study was to evaluate the effect of montelukast on clinical progress and on cytokine profiles in infants hospitalized with acute bronchiolitis.

PATIENTS AND METHODS

This was a prospective, randomized, placebo-controlled, double-blind, parallel-group study conducted in 2 medical centers.

Patients were spontaneously breathing infants who were hospitalized for bronchiolitis. Inclusion criteria were patients aged >4 weeks and <2 years with a respiratory symptom duration of <4 days were included. Symptoms of bronchiolitis include prodromal rhinorrhoea and cough, followed by at least 2 of the following signs: chest retractions, tachypnoea, wheezing, or rales. Additional inclusion criteria included first episode of wheezing or shortness of breath, randomization within 12 hours of admission and informed consent.

Exclusion criteria were any previous hospital admissions with respiratory illnesses, had ever been treated with anti-asthma medications before the current illness, corticosteroids treatment in any form during current illness, and underlying cardiopulmonary disease.

Ethics

The protocol was reviewed and approved by the local and national ethics institutional review board committees. Written informed consent was obtained from the parents or guardians. The study was registered with National Institutes of Health clinical trial database.

Clinical Evaluation

Gender, age, and medical history (including family history of asthma in first-degree relatives), previous treatments, concurrent diseases, and concomitant medications of each infant and physical examination (weight, height, body temperature, pulse rate, and respiration rate) were recorded.

Randomization

Randomization (in blocks of 4) was performed by the Edith Wolfson Medical Center's Epidemiology and Research Unit. Before randomization, subjects were stratified according to age (>3 vs <3 months). Assignment was conducted by using an online randomizer (www.randomization.com).

Allocation status was concealed in sealed envelopes. Throughout the study, the investigators, nursing and medical staff, and parents were unaware of which treatment group infants were assigned. The difference between montelukast and placebo was undetectable by sight or smell.

Intervention

Study treatment was given as montelukast (Singular) granules or matching placebo, starting in the evening of the admission day and continuing each evening until discharge. Each sachet contains as active substance montelukast (in sodium salt form) 4 mg. The excipients are mannitol, hydroxypropyl cellulose, and magnesium stearate. Inactive, identical, flavored, look-alike mannitol granules were used as placebo and were packed and sealed by the hospitals' pharmacies in identical sachets. Compliance was supervised by a study nurse and was confirmed by using sachet counts. Patients were observed for 30 minutes after ingestion of granules. If vomiting occurred, 1 additional dose was given. Acute treatment decisions during the hospital admission were taken by the departmental medical staff. The attending physician, on the basis of clinical grounds only, made the decisions to discharge subjects. The attending physician was blinded as to which study group the patient belonged.

Outcome Measures

The primary outcome was the length of stay from admission to discharge (LOS in days). Secondary outcomes included clinical score (CS) and change in cytokine levels in nasal lavage between admission and discharge days. Because the LOS may have been affected by administrative and social factors unrelated to the condition of the child, we also recorded another previously used measure of efficacy: the time until the child was "medically fit for discharge"²⁵ (had not received supplemental oxygen for 10 hours, had minimal or no chest recession, and was feeding adequately, without the need for intravenous fluids). For CS, we used the validated score described by Wang.²⁶ Follow-up evaluations including CS, pulse rate, oxygen saturation, and medical fitness for discharge were conducted by the investigators (all trained pediatricians) on enrollment and then twice per day until discharge. An additional outcome was the number of add-on treatments.

Nasal Lavage

Samples were collected at randomization and just before discharge by instilling 2.5 mL of saline in each nostril, which were then aspirated into a standard mucus extractor. Specimens were vortexed and a 500- μ L aliquot mixed with 2 mL of virus transport medium for storage at -70°C . The remaining specimen was filtered through a 100- μ m cell strainer and centrifuged at 400g[r] for 10 minutes. Supernatants were separated, aliquoted, and stored at -70°C until analysis.

Viral analysis for RSV was performed by using the "NOW" RSV rapid test (Binax Comp [Binax, Inc, Scarborough, ME]). No other viruses were tested for.

Cytokine Levels

Cytokine levels in nasal lavage supernatants were measured by Flow Cytomix Pro, (Bender Med Systems GmbH, Vienna, Austria). The following type 1 cytokines were measured: IL-2, IFN- γ , IL-12p70; type 2 cytokines were: IL-4, IL-5, IL-6, IL-10. IL-4/IFN- γ was calculated as a surrogate for Th2/Th1 ratio. Nasal washings were spun down by an Eppendorf (Hamburg, Germany) centrifuge at 10 000 rpm for 15 seconds. Twenty-five microliters of undiluted supernatant of the nasal washings were analyzed by adding 25 μ L of bead mixture with capture antibodies against each of the measured cytokines. Fifty microliters of biotinylated antibody mixture against the same cytokines was added to the bead mixture. The plate was incubated at room temperature for 2 hours on a shaker at 500 rpm. The plate was washed twice with 100 μ L of assay buffer and was incubated at room temperature for 1 hour. A total of 200 μ L of assay buffer was added to each well. The content of each well was transferred to an acquisition tube and assayed and analyzed by flow cytometry. All assays were performed in duplicate by operators blinded to patient status.

Adverse Reactions

Adverse reactions (ARs) were recorded by 1 of the private investigators, who determined the severity and causal relationship to study medications, and reported them to the institutional review board.

Statistical Methods

Data were analyzed on the intention-to-treat principle including all enrolled patients. Each variable was visually scanned for normalcy of distribution. Variables demonstrating a distribution significantly different from normal were tested by nonparametric methods. Analysis of data were conducted by using SPSS 9.0 statistical analysis software (SPSS Inc, Chicago, IL). For continuous variables, such as age and laboratory parameters, descriptive statistics were calculated and reported as mean $\pm$ SD. Normalcy of distribution of continuous variables was assessed by using the Kolmogorov-Smirnov test (cutoff at $P = .01$). Continuous variables were compared by treatment group by using the t test for independent samples or the Mann-Whitney U test, depending on the distribution of each variable. Second, posttreatment values were compared with baseline val-

ues within each treatment group using the t test for paired samples or the Wilcoxon signed ranks test as appropriate. Categorical variables such as gender and the presence of RSV were described by using frequency distributions and are presented as frequency (%). The χ^2 test was used to compare categorical variables by group. Associations between CSs and cytokines at baseline and, separately, posttreatment, were described by using Spearman's ρ correlation analysis.

General linear model (GLM)—repeated measures GLM was used to examine between-group differences in CS. All tests are 2-sided and considered significant at $P < .05$.

Sample Size

We have previously demonstrated in a similar group of 52 hospitalized infants with bronchiolitis that hypertonic inhalations decreased LOS by 25%.¹² On the basis of these data, using a similar mean LOS of 4 days (± 1.5), we calculated that there would be more than an 80% chance of detecting a clinically significant difference of 30% (1.2 day) between the groups ($\alpha = .05$) with a sample size (n) of 24 patients for each treatment group.

RESULTS

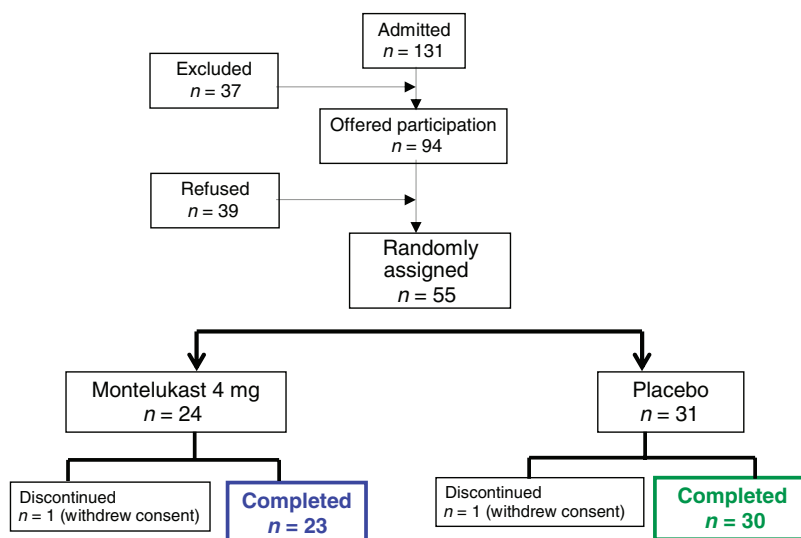
During the study period, there were 131 admissions for bronchiolitis (Fig 1). Thirty-seven of these patients were excluded, most (23) because they had received various forms of asthma medications in the past, and 39 refused participation. The remaining 55 patients were enrolled. There were no differences in baseline characteristics between those enrolled versus those excluded or whose parents refused participation. Two families withdrew their consent, thus 53 patients (aged 3.9 ± 3.7 months, 24 female) completed the study.

Baseline characteristics are shown in Table 1. Subjects had on average 3.5 days of symptoms before admission (no significant difference between groups), and the main symptom was cough. A total of 9% received bronchodilators at home during the current illness. Family history of asthma was present in 11%. There were no significant differences between the groups in terms of demographic variables, duration of wheezing, duration of coryza, the proportion of infants requiring supplemental oxygen or intravenous fluids, or the proportion of infants who proved positive for RSV. Each child received an average of 4 sachets during the study; the first 1 was administered 6.5 ± 2.1 hours from admission (difference between groups: not significant).

The primary outcome LOS was no different between the groups (mean $\pm$ SD in the placebo group was 4.63 ± 1.88 days, whereas in the montelukast group it was 4.65 ± 1.97 days), neither was the time until the child was medically fit for discharge different between the groups (placebo was 3.42 ± 1.22 days whereas in the montelukast group it was 3.52 ± 1.77 days).

CSs were similar at baseline (7.2 ± 2.4 in the placebo group versus 7.7 ± 2.3 in the montelukast group; $P = .41$); however, on discharge there was a trend for a better (lower) CS in the placebo than in the montelukast group (4.8 ± 2.2 vs 6.1 ± 2.4 , respectively; $P = .06$,

FIGURE 1
Participants' flow.



using general linear model (GLM)). Also, there was a slight tendency for the control group to recover faster than the montelukast group (Fig 2). Because of insufficient patients remaining after day 3, these differences did not reach statistical significance. Similarly, there was no difference in CS when measured at the time the child was medically fit for discharge (data not shown). LOS was positively associated with CS at baseline ($r = 0.49$; $P = .02$). There were no differences in all other secondary clinical outcomes between the groups.

Cytokine Analysis

There was no difference between the groups in both Th1 and Th2 cytokines levels at baseline. Most of the cytokines including the IL-4/IFN- γ ratio did not change significantly (see Table 2). The only cytokines that increased significantly in both groups during the study period were IL-8 and IL-6 and marginally for tumor necrosis factor α ($P = .08$). However, these cytokine responses were similar between the 2 groups.

Intergroup comparison revealed that the 2 groups did not differ significantly in any cytokines measured both at baseline and at discharge day.

The following cytokine levels were significantly positively associated with CS at baseline: IL-8 ($r = 0.62$; $P =$

.004), IL-10 ($r = 0.61$; $P = .016$), and tumor necrosis factor α ($r = 0.58$; $P = .02$), with higher cytokine levels associated with a higher CS.

IL-4/IFN- γ ratio (representing Th2/Th1) was significantly associated with CS on discharge day ($r = 0.71$; $P = .02$) but not on admission.

Additional subgroup analyses, which examined outcomes according to the presence of a family history of asthma or eczema or presence of RSV also revealed no differences (data not shown).

Ten clinical ARs were reported during the study. There were no sudden unexpected serious ARs, and no patient discontinued study participation because of an AR. The most common ARs were wheezing shortly after administration, diarrhea, and rash with no difference between the study groups. None of the ARs were determined to be drug-related.

DISCUSSION

To the best of our knowledge, this is the first randomized study to assess the effect of montelukast (Singulair) in acute bronchiolitis. The results demonstrated no benefit from montelukast therapy. None of the outcome measures (LOS, CS, saturation, cytokine levels) were different between the groups. Moreover, if there was any

TABLE 1 Baseline Characteristics

	Montelukast (n = 23)	Placebo (n = 30)	P	Total (N = 53)
Age, mo	3.2 $\pm$ 2.8	4.5 $\pm$ 4.2	.2	3.8 $\pm$ 3.5
Male/female	15:8	14:16	.9	29:24
Smoking in family, %	4.3	10.0	.2	7.5
Asthma in family, %	13.0	10.0	.7	11.3
Illness days before admission	2.9	3.9	.9	3.5
Cough before admission, %	100	100	.2	100
Bronchodilator therapy before admission, %	13.0	3.3	.3	9.0
Antibiotics before admission, %	4.3	0.0	.4	1.8
Positive for RSV, %	74	80	.4	77.3

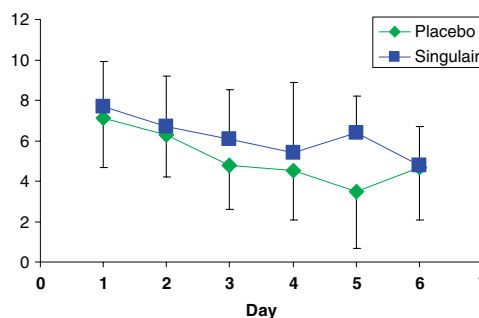


FIGURE 2
CSs during hospitalization (no significant difference at any time point).

TABLE 2 Cytokine Levels (pg/mL) in Nasal Lavage

Variable	Placebo			Montelukast		
	Baseline	Discharge	<i>P</i> , Discharge vs Baseline	Baseline	Discharge	<i>P</i> , Discharge vs Baseline
Th1						
IL-2	47.2 ± 79.3	83.9 ± 125.8	NS	61 ± 104.5	370.6 ± 1313	NS
IFN- γ	29 ± 68.7	36.4 ± 82.5	NS	41.1 ± 121.9	324.3 ± 1252	NS
IL-12	115.4 ± 256.2	61.1 ± 99.4	NS	64.1 ± 142	284.8 ± 950.3	NS
Th2						
IL-4	162.5 ± 161.5	248.6 ± 253.7	NS	153.4 ± 181	496.2 ± 1072.6	NS
IL-5	190 ± 402.1	167.5 ± 170.6	NS	178.9 ± 429.7	469.6 ± 1191.7	
IL-6	466 ± 468.5	1261.8 ± 1176.2 ^a	.02	497 ± 497.2	3764.9 ± 8626.3 ^a	.02
IL-10	63.6 ± 101.4	115.9 ± 154	NS	121.25 ± 124.1	435.6 ± 1306.7	NS
Other						
IL-1b	1347.6 ± 2464.4	1778 ± 1871.2	NS	960.9 ± 698.2	2310.2 ± 1649 ^b	.01
Tumor necrosis factor α	180.3 ± 181.4	386.1 ± 479.3	NS	262.6 ± 231.7	780.1 ± 1376	NS
IL-8	5351.6 ± 3960.5	11134.3 ± 12173.3 ^c	.01	4864.4 ± 4330.2	12371 ± 16014 ^c	.01
IL-4/IFN- γ	19.3 ± 13.8	34.96 ± 52	NS	51.7 ± 85.9	20.36 ± 26.8	

NS indicates not significant.

^a *P* = .02 versus baseline.

^b *P* = .01 versus baseline.

^c *P* = .01 versus baseline.

trend, it was always against using montelukast (CS, saturation), although no trend reached statistical significance.

Because symptoms of bronchiolitis are largely the result of airway inflammation,⁴ the mechanism-based hypothesis that montelukast therapy may have a role in this disease was plausible. Support for this possibility, albeit in asthma rather than bronchiolitis, comes from the recent study of Robertson et al²⁴ who showed a beneficial effect when montelukast was initiated at the onset of respiratory symptoms and continued for at least 7 days. Bisgard et al²² showed that montelukast increased the number of symptom-free days and delayed the recurrence of wheeze in the month after RSV-induced wheezing in children aged 3 to 36 months. Subsequently, in children aged 2 to 5 years with frequent episodic asthma, primarily viral induced, regular therapy with daily montelukast for 12 months reduced exacerbations by 31%, delayed the time to the first exacerbation, and lowered the need for inhaled corticosteroids.²³ In addition, montelukast has been demonstrated to be efficacious as an acute episode modifier in children aged 2 to 14 years, with virus-induced wheezing where it was prescribed at the onset of a viral infection.²⁴ However, despite this supporting rationale, the results of the present study failed to demonstrate clear benefit for montelukast in acute bronchiolitis. These results are similar to those reported in a previous study, in which montelukast had no effect on the duration or severity of viral-induced exacerbations of wheezing, although there was a tendency toward a reduced exacerbation rate.²⁷ Furthermore, even the Bisgard et al²² study showed no beneficial effects of montelukast in the first 2 weeks after bronchiolitis.

Previous studies of montelukast in young children were all done with chewable tablets. Recently, montelukast was approved for use in infants over 1 year in the form of

granule sachets, and the present study is the first 1 to evaluate clinically the effects of montelukast granules.

The patients reported in this study are the youngest yet reported, with a mean age of 3.9 months. The median age in the Bisgard et al study population was 9 months, and it included children up to 36 months.²² Straub et al²⁸ studied the effect of montelukast in 24 infants aged 10 to 26 months. In contrast to the previous study where montelukast 5 mg was administered to infants recovering from bronchiolitis,²² our study is the first to our knowledge in which montelukast was administered from the first day of admission, during the acute phase of the disease. This report is also the first to our knowledge to include details of the Th2 and Th1 cytokines and their ratio in an intervention study of bronchiolitis. No difference was observed between the 2 groups at baseline and during the time scale of our study.

There are a number of possible reasons why montelukast was ineffective, including administration failure, different pharmacokinetics in infants, too short a time period of therapy, insufficient power to detect differences, or that montelukast treatment is indeed not effective. Administration failure is unlikely, because there were no failures in administering the granules. Compliance with therapy was 90%, on the basis of the final sachet count, and all the infants swallowed the granules without significant difficulty or vomiting. Pharmacokinetics in infants may differ, particularly in bronchiolitis. It is possible that the plasma level of the drug did not reach therapeutic levels because of reduced absorption, increased metabolism, or interference with other metabolites. A recent study reported similar pharmacokinetic behavior of montelukast in young (median age: 4 months) versus older infants.²⁹ Because of the different pathogenetic mechanisms of bronchiolitis compared with asthma and healthy infants, these recent observations may not apply.

A longer period of administration may have resulted in a better outcome. Support for this speculation may come from the study of montelukast in postbronchiolitis where a longer period of administration was employed. However, we felt it was unethical to prescribe therapy for more than the hospital stay when the primary objective was LOS. The study was sufficiently powerful to detect a significant clinical effect if it had been present. Moreover, any trend demonstrated was indeed against using montelukast in the acute phase, so additional increasing the number of subjects would probably not have changed the conclusion in favor of montelukast.

As Legg and colleagues²⁰ previously reported, an imbalance in cytokine species, with excessive type 2 over type 1 species, is seen in acute bronchiolitis, and our study confirms this. This is best demonstrated by a high IL-4/IFN- γ ratio. We found, however, that the absolute cytokine levels were higher than those reported by Legg et al.²⁰ Various methodologic differences between the studies may be account for these differences: (1) Different assay kits with different sensitivities were used in the 2 studies; (2) The clinical presentation of our patients differed markedly from those in Legg et al's study: In the Legg study, only 9 of the 28 RSV-positive infants developed symptoms and signs of acute bronchiolitis, only 3 required hospitalization, and the remaining 19 infants had signs of an upper respiratory tract infection alone. In contrast, all our patients had moderate to severe bronchiolitis and all required hospitalization. (3) Our patients were considerably younger: 3.8 ± 3.5 months versus 7 ± 4 months in Legg et al's study. This may have driven the type 2 cytokine levels upward, reflecting the immaturity of the immune system.

From a mechanistic view, a distinction may be made between the effect of montelukast on innate versus adaptive immunity. A recent study suggested that montelukast corrected Th2/Th1 imbalance when administered after RSV bronchiolitis.³⁰ Thus, whereas montelukast probably has a positive effect on late-adaptive immune inflammatory, postbronchiolitis response (especially type 2-like inflammation), it may not benefit early innate immunity (during the viral shedding phase). Thus, montelukast may be effective after the viral clearance phase and be of no value (or even deleterious) during the replication and shedding phase of the disease (similar to suggested effect of exogenous steroids). The cytokine results, including IL-4/IFN- γ ratio, did not support the hypothesis that montelukast may favorably alter the Th2/Th1 ratio in the acute phase of bronchiolitis.

Considering this and previous studies, we believe that although montelukast is probably active in later phases when adaptive immunity occurs, it is not effective in the acute phase of bronchiolitis, when innate immunity-related cytokines and inflammation are still dominant. Recently Bennett et al³¹ made observations suggesting that high levels of certain cytokines may be protective in acute bronchiolitis. Our present study may have lacked the statistical power to detect modest but real differences in cytokines; nevertheless, it did provide the interesting observation that the levels of many of the cytokines in

the montelukast group tended to be markedly higher at discharge when compared both with the baseline montelukast group and to the discharge placebo group. In light of these differences, we believe that additional studies of cytokine responses to montelukast in acute bronchiolitis should be performed.

Some limitations should be acknowledged. Montelukast therapy was not initiated at the onset of illness. We excluded patients who had >4 days of symptoms before admission. Because we aimed to study hospitalized patients, the results may be limited only to more severe patients. Nevertheless, we see no reason to believe that montelukast will be of clinical benefit in milder cases. An outpatient study, in which patients are treated as soon as the diagnosis of bronchiolitis is made, may be interesting (although it may be impractical). Of note is that the present study evaluated only short-term effects of montelukast. Montelukast therapy may be associated long-term effects on asthma development, but such effects were beyond the scope of the present study. The lack of systematic virology testing may be a limitation. With regard to cytokine levels, we recognize that the nasal lavage technique has its drawbacks (ie, unknown dilution of the secretions).³² In the present study, we used a number of samples taken from patients as their own controls, which may have reduced this concern. Cytokine levels in lower airways may have been more compelling than nasal lavage samples. However, because nasal inflammatory processes have been shown to reflect those in the lower airways^{33,34} and because nasal lavage technique is relatively noninvasive and is well tolerated by infants, it was ethically the best-suited method for this study.

CONCLUSIONS

Montelukast granules administered to infants hospitalized with acute bronchiolitis did not influence the clinical course. Although montelukast therapy was associated with a trend toward higher cytokine levels, no significant beneficial effect on cytokine levels could be demonstrated. This study does not support the use of montelukast in infants with bronchiolitis during the acute phase.

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