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RCT of Montelukast as Prophylaxis for Upper Respiratory Tract Infections in Children

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KEY WORDS

children, leukotriene-receptor antagonist, montelukast, upper respiratory tract infection

ABBREVIATIONS

RSV—respiratory syncytial virus
URI—upper respiratory tract infection

This trial has been registered at www.clinicaltrials.gov (identifier NCT00551382).

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WHAT'S KNOWN ON THIS SUBJECT: Upper respiratory tract infections (URIs) are very common in children. Currently, there are no effective preventive measures for URI. There are no studies on the effect of montelukast for prevention of URI.

WHAT THIS STUDY ADDS: In a randomized, double-blind, placebo-controlled study of preschool-aged children, 12-week prophylactic treatment with montelukast did not reduce the incidence of URI.

abstract

BACKGROUND: Infections with viruses causing upper respiratory tract infection (URI) are associated with increased leukotriene levels in the upper airways. Montelukast, a selective leukotriene-receptor antagonist, is an effective treatment of asthma and allergic rhinitis.

OBJECTIVE: To determine whether prophylactic treatment with montelukast reduces the incidence and severity of URI in children.

METHODS: A randomized, double-blind, placebo-controlled study was performed in 3 primary care pediatric ambulatory clinics in Israel. Healthy children aged 1 to 5 years were randomly assigned in a 1:1 ratio to receive 12-week treatment with 4 mg oral montelukast or look-alike placebo. Patients were excluded if they had a previous history of reactive airway disease. A study coordinator contacted the parents by phone once a week to obtain information regarding the occurrence of acute respiratory episodes. The parents received a diary card to record any acute symptoms of URI. The primary outcome measure was the number of URI episodes.

RESULTS: Three hundred children were recruited and randomly assigned into montelukast (n = 153) or placebo (n = 147) groups. One hundred thirty-one (85.6%) of the children treated with montelukast and 129 (87.7%) of the children treated with placebo completed 12 weeks of treatment. The number of weeks in which URI was reported was 30.4% in children treated with montelukast and 30.7% in children treated with placebo. There was no significant difference in any of the secondary variables between the groups.

CONCLUSIONS: In preschool-aged children, 12-week treatment with montelukast, compared with placebo, did not reduce the incidence of URI. *Pediatrics* 2012;129:e285–e290

Viral upper respiratory tract infection (URI) is one of the most common diseases among toddlers and preschool-aged children. In the United States, approximately 25 million patients with URI are treated in the ambulatory care setting annually.[1] In 1996, almost 2 million visits to emergency departments in the United States were due to URI.[2]

In a survey among Canadian toddlers,[3] during fall and winter, children suffered from cold symptoms 23.4% of the time. One in four children less than 5 years of age was reported to have had URI in the previous 2 weeks.[4] The average duration of a URI episode ranges between 6.6[5] and 12.1 days.[3] Almost half of children aged 4 to 5 years suffer from more than 2 episodes of URI annually.[6] Currently, there are no effective preventive measures for URI.[7–9] Because many viral agents may cause URI, no single vaccine is available, and because there is no known common antigen for these viruses, it is unlikely that such a vaccine will be developed.

Montelukast is a selective leukotriene-receptor antagonist that inhibits the cysteinyl leukotriene 1 receptor. It is well tolerated in young children.[10] It is an effective treatment of asthma[11–18] and allergic rhinitis in adult and pediatric patients.[19,20] Infections with viruses causing URI, such as influenza A, rhinovirus, and respiratory syncytial virus (RSV), increase leukotriene levels in nasal secretions.[21] The effect of montelukast as a treatment of nonspecific cough has not been adequately studied,[22] and there are no studies on the effect of montelukast for prevention of URI.

The study hypothesis was that prophylactic treatment with montelukast will reduce the incidence and severity of URI in children.

METHODS

Design

A randomized, double-blind, placebo-controlled study was performed in 3 primary pediatric ambulatory clinics in central Israel. The study was approved by the hospital and the Israeli health ministry ethics boards and was registered with clinicaltrials.gov as NCT00551382.

Patients

Healthy children aged 1 to 5 years were recruited. Patients were excluded if they had a previous history of reactive airways disease (defined as a history of treatment with bronchodilators in the previous 3 months or more than 1 treatment in the past year, hospital admission due to reactive airways disease, or prophylactic use of montelukast or steroids), chronic cardiac or respiratory disease, history of allergic rhinitis, or were taking chronic medications of any kind. Patients were also excluded if there was a known allergy to montelukast or if they had an active URI within the 7 days before consideration for the study.

Intervention

Patients underwent physical examination by their pediatrician and were assessed for eligibility. Using a computerized random number generator, an allocation sequence was created. The allocation sequence was kept in serially numbered, opaque, sealed envelopes. Eligible patients were randomly assigned in a 1:1 ratio to receive 12-week treatment with 4 mg oral montelukast (Singulair; Merck& Co. Inc, Whitehouse Station, NJ) (as tablet or granules) or look-alike placebo. The caregivers and the investigators were blinded to the study product.

At the outset of the study, the parents received a drug box containing either montelukast or look-alike placebo. They also received a diary card to record any acute symptoms of URI, any other specific symptoms (fever, rhinitis, and cough), use of antipyretic or antibiotic agents, absence from kindergarten, and unscheduled physician office visits. The study coordinator instructed the families on the use of the diaries, which were collected at the conclusion of the study.

A study coordinator contacted the parents by phone once a week to obtain information on the occurrence of acute respiratory episodes and to ensure compliance. She also reviewed the pediatricians' appointment books and the childrens' electronic medical charts to identify unscheduled physician appointments and to record various medications administered during the study period.

URI was defined as the appearance of at least 2 of the following 5 symptoms: sneezing, coughing, nasal congestion, runny nose, or fever (temperature $>38.0°C$). Duration of URI was measured from the first day until the last day before all symptoms had disappeared for at least 2 consecutive days.

Outcome Measures

The primary outcome measure was the number and duration of URI episodes. Secondary outcome measures included incidence of respiratory system infections (acute otitis media, pneumonia, tonsillitis, or pharyngitis). Other secondary measures were the number of weeks in which the child had fever, used antibiotic or antipyretic drugs, had unscheduled visits to the physician's office, was absent from day care or kindergarten, the number of days of parental absence from work because of a child's illness, hospital admissions, and adverse reactions to the drug.

Statistical Analysis

The Student's t test or the Mann–Whitney tests (as appropriate) were used for continuous variables. The χ^2 or Fisher exact tests were used as appropriate for comparisons of categorical variables. The possibility of differing efficacy by age and/or gender were analyzed by analysis of variance (for continuous variables) or by the Breslow–Day test (for categorical variables).

Sample Size

Because we assumed the mean duration of an untreated episode of URI to be 5 to 7 days, with an SD of 6 days,[5] approximately 500 children were needed to detect 1.5 to 2 days' difference in URI duration between patients treated with montelukast and those treated with placebo, with a power of 80% (2-tailed α level .05). The 1.5 to 2 days' difference in URI duration was chosen as a significant difference based on our clinical experience.

RESULTS

An interim analysis was conducted because of difficulties in patient recruitment.

Three hundred children were recruited and randomly assigned into montelukast (n = 153) or placebo (n = 147) groups. One hundred thirty-one (85.6%) of the children treated with montelukast and 129 (87.7%) of the children treated with placebo completed 12 weeks of treatment (see Fig 1). The mean patient age was 3.33 ± 1.43 years and 3.4 ± 1.46 years in the montelukast and placebo groups, respectively. There were no significant differences in the clinical and demographic characteristics between the two groups (Table 1).

For all the children who completed the study, data obtained by the research coordinator was available for all 12 weeks. Data are presented as weeks in which the parents reported the occurrence of symptoms. The number of weeks in which URI was reported was 30.4% in children treated with montelukast and 30.7% in children treated with placebo (P = .83). The median number of URI episodes was similar in both groups. There was no significant difference between the groups in any of the secondary variables (Table 2).

Only 53 (34.6%) parents of children treated with montelukast and 55 (37.4%) parents of children treated with placebo completed the parents' diaries. There were no significant differences in age, gender, and number of siblings in the family between those who completed the dairies and those who did not keep the diaries. The number of reported URI episodes during the study period was 2.7 ± 2.2 in children treated with montelukast and 2.4 ± 2.9 in children treated with placebo (P = .14).The duration of URI episodes did not differ between the groups (7.4 ± 7 days and 6.1 ± 5.5 days, respectively, P = .37). The number of fever episodes and the number of days that antibiotics and antipyretics were used was higher in children treated with montelukast compared with those in children treated with placebo (Table 3).

Adverse events were reported in 18 (12.7%) children treated with

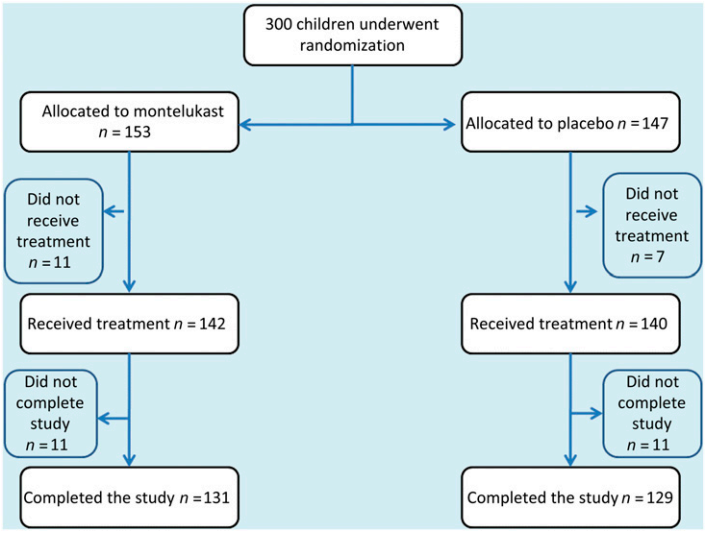

FIGURE 1
Randomization and allocation of patients.

TABLE 1 Sociodemographic Data of Participants

Parameter	Montelukast Group (n = 153)	Placebo Group (n = 147)
Child's age (y) ± SD	3.33 ± 1.43	3.40 ± 1.46
Male gender, *n*	82 (53.6%)	85 (57.8%)
Weight (kg) ± SD	13.87 ± 3.60	13.95 ± 3.50
Father's age (y) ± SD	34.51 ± 6.61	35.78 ± 7.71
Mother's age (y) ± SD	30.00 ± 6.10	30.86 ± 5.67
Father's schooling (y) ± SD	10.03 ± 2.28	10.29 ± 2.62
Mother's schooling (y) ± SD	10.66 ± 2.39	10.57 ± 2.46
Father smokes, *n*	90 (60.8%)	86 (60.6%)
Mother smokes, *n*	9 (5.9%)	14 (9.7%)
Number of persons in family ± SD	5.70 ± 2.00	6.14 ± 2.35
Number of children in family ± SD	3.76 ± 2.08	4.20 ± 2.35
Child's birth order, *n*	1st (39, 25.5%)	1st (33, 22.5%)
	2nd (34, 22.2%)	2nd (26, 17.7%)
	3rd (22, 14.4%)	3rd (31, 21.1%)
	≥4th (58, 37.9%)	≥4th (57, 38.8%)
Number of rooms in dwelling ± SD	3.07 ± 1.00	3.23 ± 1.09
Child's medical history, *n*		
Premature birth	5 (3.3%)	6 (4.1%)
Previous hospitalization	41 (26.8%)	37 (25.2%)
Previous stridor event	11 (7.2%)	12 (8.2%)
Previous radiograph-confirmed pneumonia	21 (13.7%)	27 (18.4%)
Attending day care	90 (58.8%)	86 (58.5%)

TABLE 2 Outcome Variables From Coordinator Follow-up

Parameter	Montelukast Group, % (n = 153)	Placebo Group, % (n = 147)	Univariate Significance[a]
Data obtained by telephone interview			
Fever	8	6.7	0.34
Parent reported URI episode	30.7	30.4	0.83
Absence from kindergarten	5.1	4.5	0.54
Parent work days lost because of child's illness	3.1	1.6	0.12
Adverse events	1.9	1.6	0.73
Drug adherence	98.8	98.8	0.5
Unscheduled visit to physician's office	10.7	9	0.24
Admission to hospital	0.2	0	0.083
Data obtained from the child's medical record			
Use of antibiotics	3.7	3	0.23
Pneumonia	1.1	0.7	0.19
URI episode	4.9	3.5	0.22
Acute otitis media episode	1.1	0.5	0.089
Tonsillitis or pharyngitis episode	2	1.5	0.24

For each parameter and for each subject, the percentage of weeks where the answer was "yes" was calculated. These percentages were averaged over the subjects in each group, weighting each subject by the number of weeks where an answer was obtained.

[a] By Student's *t* test.

TABLE 3 Outcome Variables From Diaries of Parents

Parameter	Montelukast Group (n = 53)	Placebo Group (n = 55)	Univariate Significance[a]
Number of URI episodes ± SD	2.72 ± 2.21	2.42 ± 2.91	.14
Average duration of URI episode (d) ± SD	7.43 ± 7.04	6.10 ± 5.55	.37
Number of febrile episodes ± SD	1.51 ± 1.50	1.05 ± 1.37	.047
Average duration of febrile episodes (d) ± SD	2.24 ± 1.50	1.78 ± 0.94	.19
Use of antibiotics (number of d) ± SD	3.60 ± 4.89	1.96 ± 3.73	.0489
Use of antipyretic drugs (number of d) ± SD	3.30 ± 3.60	2.01 ± 2.96	.0417
Missed kindergarten (number of d) ± SD	2.02 ± 3.42	1.05 ± 2.46	.1484

[a] By Mann–Whitney test.

montelukast and in 17 (12.1%) children treated with placebo. One child treated with montelukast experienced a rash. Therapy with montelukast was discontinued by the patient's mother after 2 days of therapy. Five days later, the patient experienced seizures and was hospitalized. He was diagnosed with epilepsy and withdrawn from the study. Three other children (one with diarrhea, vomiting, and fever, the second with wheezing, and the third with restlessness) were admitted to the hospital during the study period. These patients were treated with montelukast. All other adverse reactions were mild, and there was no need to discontinue the drug (Table 4).

TABLE 4 Adverse Events as Reported by the Parents

Parameter	Montelukast Group, n (%) (n = 142)[a]	Placebo Group, n (%) (n = 140)[a]	Univariate Significance[b]
Diarrhea	5 (3.5)	7 (5)	.57
Vomiting	3 (2.1)	2 (1.4)	1
Abdominal pain	2 (1.4)	5 (3.5)	.28
Rash	4 (2.8)	2 (1.4)	.68
Other[c]	4 (2.8)	3 (2.1)	1
Total	18 (12.7)	17 (12.1)	1

[a] Number of patients who took the drug.

[b] By Fisher exact test.

[c] Fatigue, loss of appetite, restlessness, lethargy, and constipation.

DISCUSSION

In a large, randomized, controlled study of preschool-aged children, 12-week treatment with montelukast did not reduce the incidence or duration of URI episodes. There were no significant differences between the groups in the number of unscheduled medical appointments or in the number of days parents missed work because their child suffered from URI.

Viral URI is extremely common among infants and preschool-aged children.[1–6] Infants were not included because the lower age limit approved for use of montelukast in Israel is 1 year. URI is associated with complications such as lower respiratory infection, otitis media,[23] and asthma.[24] There are also significant costs incurred as a result of viral URI in children.[3] The occurrence of symptomatic rhinovirus illnesses during infancy is associated with increased risk for wheezing at an older age.[25] Currently, there is no effective treatment of URI.

Leukotrienes are lipid mediators of inflammation, and leukotriene levels are increased in viral infections of the respiratory system. In mice infected with influenza virus, leukotriene B4 levels in the lungs peaked 36 hours postinfection.[26]

Elevated levels of leukotriene C4 were found in infants with RSV bronchiolitis and URI.[27] The concentrations of leukotrienes in nasal lavage fluid were significantly higher in infants with RSV bronchiolitis than in healthy controls, with the levels remaining elevated a month after the acute infection.[28]

Interleukin 8 induces leukotriene secretion.[29] In adults infected with rhinovirus, interleukin 8 levels in nasal secretions were significantly higher in symptomatic patients than in asymptomatic patients. There was a significant correlation between interleukin 8 and the severity of URI symptoms.[30]

In an experimental model, healthy volunteers were infected with influenza A, rhinovirus, and RSV.[21] Leukotriene 4 levels in nasal secretions increased, and there was a temporal association between the symptoms and leukotriene levels. In a retrospective analysis of adult asthma patients, treatment with leukotriene-receptor antagonist was associated with lower incidence of common cold-like symptoms.[31]

These findings formed the basis for the rationale of the current study. We did not measure leukotriene levels in the participants, so it is not clear whether montelukast reduced the systemic or local leukotriene levels. However, our findings clearly indicate that the leukotriene inhibitor montelukast did not reduce the number of URI episodes in preschool-aged children and did not reduce the incidence of any of the complications that were evaluated.

It has been postulated that montelukast may have a role in the treatment of children with otitis media.[32] Although the focus of the current study was not on otitis media, it was one of the secondary outcomes. The treatment did not significantly reduce the incidence of otitis media.

Although there was no difference between the groups in the incidence of URI, based on parents' diaries, children treated with montelukast had more episodes of fever and were more often treated with antibiotics. The differences between groups were small with marginal statistical significance, and their clinical implication is not clear.

Montelukast is an effective prophylactic treatment of asthma. In the current study, children with a history of reactive airway disease were excluded to reduce potential confounders. There are numerous studies on the effect of montelukast in children with conditions other than asthma. In children with bronchiolitis, montelukast yielded mixed results. In a double-blind study of 3- to 24-month-old children with bronchiolitis, montelukast did not improve respiratory symptoms of post–RSV bronchiolitis.[33] In contrast to those findings, Kim et al[34] reported a significantly lower risk for recurrent wheezing episodes at 12 months in children with bronchiolitis treated with montelukast.

In patients with cystic fibrosis, montelukast reduces eosinophilic inflammation[35] and is associated with decreased cough and wheezing.[36]

The number of reported adverse events was low and did not differ between children treated with montelukast and those treated with placebo. All the reported adverse effects were mild. The low incidence of adverse events is similar to findings from previous studies[33] and is another indication of the safety of the drug, even in young children.

The study was conducted in several communities in central Israel characterized by low socioeconomic profile and large families. Smoking was relatively common in these families. The study results should be interpreted with caution in other settings.

Our study has several limitations. Recorded adherence to treatment was based on parental report with no objective verification; a major limitation was the fact that only 35% of the parents completed the parents' diaries. The reason for the poor compliance with the diaries is not clear. It may have resulted from the complexity of the diaries and the long duration of the study. Because we anticipated that some parents would not complete the diaries, the study protocol included other measures for determining the frequency of URI. The characteristics of patients for whom parental diaries were completed were similar in both groups and did not significantly differ from those of all the other patients, suggesting that this group is representative of the entire sample.

The data from the coordinator reports is presented as percentage of weeks where the answer was "yes." It is an average that can give the same value for different situations. However, it is unlikely that the main outcome (ie, weeks with URI) was effected because the median number of URI episodes was similar in both groups.

The sample size calculation was based on data that could not be obtained by the weekly follow-up of the research coordinator. However, because there was no trend for better outcome with montelukast, it is unlikely that a larger sample would have shown significant benefits for the drug.

CONCLUSION

In a large, randomized, placebo-controlled study of preschool-aged children, 12-week treatment with montelukast did not reduce the incidence of URI.

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