ORIGINAL ARTICLE

Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children

Francine M. Ducharme, M.D., Chantal Lemire, M.D., Francisco J.D. Noya, M.D., G. Michael Davis, M.D., Nathalie Alos, M.D., Hélène Leblond, M.D., Cheryl Savdie, M.Sc., Jean-Paul Collet, M.D., Ph.D., Lyudmyla Khomenko, Ph.D., Georges Rivard, M.D., and Robert W. Platt, Ph.D.

ABSTRACT

BACKGROUND

Although virus-induced wheezing is common in preschool-age children, optimal management remains elusive. We examined the efficacy and safety of preemptive treatment with high-dose fluticasone in reducing the severity of recurrent virus-induced wheezing in children.

METHODS

We randomly assigned 129 children who were 1 to 6 years of age to receive 750 μg of fluticasone propionate (ex-valve [manufacturer-measured] dose) or placebo twice daily, beginning at the onset of an upper respiratory tract infection and continuing for a maximum of 10 days, over a period of 6 to 12 months. The primary outcome was rescue oral corticosteroid use. Secondary outcomes included symptoms, use of β_2-agonists, acute care visits, hospitalizations, discontinuation of the study drug, change in growth and bone mineral density, basal cortisol level, and adverse events.

RESULTS

Over a median period of 40 weeks, 8% of upper respiratory tract infections in the fluticasone group led to treatment with rescue systemic corticosteroids, as compared with 18% in the placebo group (odds ratio, 0.49; 95% confidence interval [CI], 0.30 to 0.83). Children who were treated with fluticasone, as compared with those who were given placebo, had smaller mean (±SD) gains from baseline in height (6.23±2.62 cm [unadjusted value]; z score, −0.19 ±0.42 vs. 6.56±2.90 cm [unadjusted value]; z score, 0.00±0.48; difference between groups in z score from baseline to end point, −0.24 [95% CI, −0.40 to −0.08]) and in weight (1.53±1.17 kg [unadjusted value]; z score, −0.15±0.48 vs. 2.17±1.79 kg [unadjusted value]; z score, 0.11±0.43; difference between groups in z score from baseline to end point, −0.26 [95% CI, −0.41 to −0.09]). There were no significant differences between the groups in basal cortisol level, bone mineral density, or adverse events.

CONCLUSIONS

In preschool-age children with moderate-to-severe virus-induced wheezing, preemptive treatment with high-dose fluticasone as compared with placebo reduced the use of rescue oral corticosteroids. Treatment with fluticasone was associated with a smaller gain in height and weight. Given the potential for overuse, this preventive approach should not be adopted in clinical practice until long-term adverse effects are clarified. (ClinicalTrials.gov number, NCT00238927.)

From the Applied Clinical Research Unit, Research Centre, Centre Hospitalier Universitaire Sainte-Justine, and the Department of Pediatrics, University of Montreal, Montreal (F.M.D., N.A., C.S., L.K.); the Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal (R.W.P.); the Department of Pediatrics, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke (C.L.); the Department of Pediatrics, Research Institute of the Montreal Children's Hospital, McGill University Health Centre, Montreal (F.J.D.N., G.M.D.); Department of Pediatrics, Hôpital Maisonneuve–Rosemont, University of Montreal, Montreal (H.L.); and the Department of Pediatrics, Université Laval, Quebec (G.R.) — all in Quebec, Canada; and the Departments of Pediatrics and of Healthcare and Epidemiology, University of British Columbia, Vancouver, Canada (J.-P.C.). Address reprint requests to Dr. Ducharme at the Department of Pediatrics, Centre Hospitalier Universitaire Sainte-Justine, Rm. 7939, University of Montreal, 3175 Côte Sainte-Catherine, Montreal, QC H3T 1C5, Canada, or at francine.m.ducharme@umontreal.ca.

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Upper respiratory tract infections account for more than 80% of wheezing episodes in children.[1,2] With more than 30 acute care visits per 1000 population, preschool-age children have a rate of acute care visits for asthma that is higher by a factor of three than that for school-age children and adults.[3,4] Most children wheeze only when they have upper respiratory tract infections, are usually nonatopic, and outgrow symptoms by 6 years of age.[5-7] Yet, since preschool-age children have 6 to 10 upper respiratory tract infections each year,[8] recurrent virus-induced wheezing is associated with considerable distress and use of health care services. The optimal preventive management remains elusive, particularly for children with moderate-to-severe episodes.[9-11]

Randomized, placebo-controlled trials have examined five principal strategies for the secondary prevention of recurrent virus-induced wheezing.[10] Oral corticosteroids at the onset of an upper respiratory tract infection, a treatment suggested by Brunette and colleagues,[12] was not proved to be superior to placebo,[13,14] and there has been concern about the safety profile.[15] Preemptive use of leukotriene-receptor antagonists reduced symptoms and decreased the number of emergency room visits,[16] and maintenance use reduced the rate of exacerbations[17]; however, neither preemptive nor maintenance use reduced rescue oral corticosteroid use in a diverse group of patients, including school-age children[16] and children with persistent asthma.[17] A Cochrane review[18] examined the efficacy of inhaled corticosteroids. Maintenance therapy was no more effective than placebo,[19-21] but preemptive high-dose therapy appeared to be promising, with a statistically nonsignificant but clinically important 20%[22] to 50%[23,24] reduction in the use of rescue oral corticosteroids. In this proof-of-concept trial, we hypothesized that high-dose inhaled fluticasone propionate initiated at the onset of an upper respiratory tract infection would be effective in decreasing the severity of episodes of virus-induced wheezing in preschool-age children.

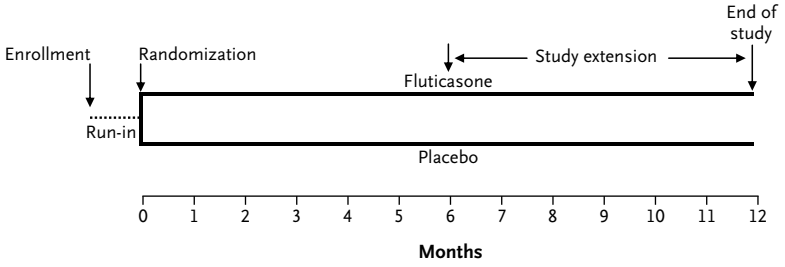
METHODS

STUDY DESIGN AND PATIENTS

We conducted a parallel-group, randomized, placebo-controlled trial with triple blinding (parents, physicians and nurses, and biostatisticians) in five institutions in Quebec. The institutional review board at each site approved the study. Parents gave written informed consent for study participation. GlaxoSmithKline (Canada), one of the main sponsors of the study, and the public funding agencies had no input in the design and conduct of the study, the analysis of the data, or the preparation of the manuscript; the academic authors vouch for the accuracy and completeness of the reported data.

Children who were 1 to 6 years of age were eligible if they had had three or more wheezing episodes in their lifetime, seemingly triggered exclusively by upper respiratory tract infections; if they had no intercurrent symptoms; if they had received at least one course of rescue systemic corticosteroids — a marker of moderate exacerbation[5] — in the previous 6 months (or two in the preceding 12 months); and if their parents were fluent in French or English. Hospital admission, a common marker of severe exacerbations, was not a prerequisite for enrollment. Exclusion criteria were prior intubation for a respiratory illness, neonatal respiratory conditions, other chronic diseases, suspected allergic rhinitis,[25] and allergies to aeroallergens, documented by a positive skin test or elevated specific IgE levels.

The study design and schedule are shown in Figure 1. After randomization, a medical visit was scheduled every 4 months to monitor symptoms, growth, and adverse events. At each visit, symptom control and adverse health events were documented, and the child was weighed and measured on an upright stadiometer (Health-o-Meter PRO Series, Sunbeam). Lumbar (L2 to L4) bone mineral content (in grams) and bone mineral density (in grams per square centimeter) were ascertained at baseline and at the end of the study period (or at the last visit, in the case of children whose parents withdrew them from the study) with the use of the Lunar DPX-IQ (GE Healthcare). Bone age was also measured at these two times. Scan quality and measurements were reviewed by an independent radiologist who was unaware of the treatment assignment. Basal serum cortisol level, sampled before 8 a.m. at baseline and at the end of the study, was measured with the Immulite assay (Diagnostic Products). Serum IgE levels, as well as varicella latex agglutination antibodies in susceptible children, were



Telephone Contacts													
URTI and related events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse health events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Protocol review		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Exchange of diary and study inhalers	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medical Visits														
Symptoms		✓				✓				✓				✓
Adverse health events		✓				✓				✓				✓
Height and weight		✓				✓				✓				✓
Laboratory Tests														
Bone mineral density and bone age		✓												
Basal cortisol		✓												✓
IgE and varicella antibodies		✓												✓

Figure 1. Study Design and Schedule of Procedures.

Eligible participants entered a 7-to-14-day run-in period to confirm the recent use of systemic corticosteroids and the absence of intercurrent symptoms and β_2-agonist use, as recorded with both a diary and a dose counter. The run-in period started at least 21 days after the last dose of maintenance asthma medication or oral corticosteroid. A maximum of three run-in periods was allowed only for children who had upper respiratory tract infections (URTIs) during this period. After randomization, the study nurse made monthly telephone contacts with parents to gather information on URTIs, drug use, and related use of health care resources; to ascertain adverse health events; to review the protocol, ascertain the presence of symptoms of a URTI during wheezing illnesses and the absence of intercurrent symptoms, and assess the appropriateness of study-drug initiation; and to plan the exchange of the diary and study inhalers.

documented at the time of randomization to plan appropriate prophylaxis in case of exposure.

Admission to an intensive care unit, chronic symptoms, poor control of exacerbations, use of the study drug for more than 15 days per month for 3 months, or perceived lack of efficacy led to discontinuation of the study drug. On the recommendation of an independent advisory board, the study period, which had been set at a mean (±SD) of 6±1 months, was extended to 12±2 months in November 2002 because of slow recruitment.

At the first sign of an upper respiratory tract infection (e.g., rhinorrhea, nasal congestion, sore throat, or earache), parents administered three inhalations of the study drug — 250 μg of fluticasone propionate (ex-valve [manufacturer-measured]) per inhalation — or placebo twice daily, until 48 hours had elapsed with no symptoms of cough or wheezing. If symptoms of cough, wheezing, or dyspnea developed, parents administered two to four inhalations of 100 μg of albuterol hydrofluoroalkane (Ventolin HFA, GlaxoSmithKline) every 4 hours as needed. If symptoms lasted longer than 10 days, the parents informed the research nurse, who made arrangements for a medical consultation. Both the study drug and albuterol inhalers were fitted with a dose counter (Doser CT, Meditrack) to allow for daily monitoring of the use of study inhalers without revealing the recorded doses.[26] We reviewed the inhalation technique with the parents and provided an age-appropriate spacer with mask or mouthpiece for the children (AeroChamber, Trudell Medical International). Clearing of nasal passages with salty water was recommended to minimize postnasal drip. No additional asthma treatments were permitted, other than rescue systemic corticosteroids.

OUTCOMES

The primary outcome was the group rate of short courses of systemic corticosteroids, confirmed by hospital or pharmacy records or both. Secondary efficacy outcomes included upper respiratory tract infections with symptoms of cough, wheezing, or dyspnea; acute care visits and hospitalizations for wheezing; discontinuation of the study drug; duration and intensity of symptoms[27]; and use of rescue β_2-agonists. The effect on parents was assessed for each upper respiratory tract infection with the use of three methods: a global assessment on a 7-point Likert scale (which was based on parents' responses at the end of the episode to the question, "Overall, how much did this asthma flare-up affect you?"; responses ranged from 1 ["not at all"] to 7 ["extremely"]); a record of the number of days of missed work (or usual activities); and the score on the Paediatric Asthma Caregiver's Quality of Life Questionnaire, developed by Juniper et al.[28] (a 13-item questionnaire, in which the score for each item ranges from 1 to 7, with higher scores indicating better quality of life; a value of 0.5 on a 7-point Likert scale indicates a minimally important group difference[28,29]). For each information source (monthly contact, diary, dose counter, and questionnaires), only upper respiratory tract infections for which complete data were available were included in the analysis. Safety measures included the change from baseline in height, weight, and bone mineral density, reported as z scores adjusted for age and sex[30,31]; change in bone age[32]; adverse events; and basal cortisol level, with values below 138 nmol per liter (5.0 μg per deciliter) considered to be depressed.[33]

RANDOMIZATION AND BLINDING

With the use of a central computerized procedure, we randomly assigned children to receive fluticasone or placebo, in permuted blocks of four, stratified according to center (of which there were five) and type of spacer (mouthpiece or mask); opaque sealed envelopes contained the assignment code. Parents were provided with a coded metered-dose inhaler containing 250 μg of hydrofluoroalkane (HFA)-propelled fluticasone propionate or with a coded metered-dose inhaler containing placebo, which looked identical in all respects to the fluticasone inhaler (GlaxoSmithKline). The randomization code was disclosed after the completion of preliminary analyses. At the end of follow-up, each child's parent, nurse, and physician were independently asked to guess the child's group assignment.

STATISTICAL ANALYSIS

We estimated that with 64 children per group, the study would have 80% power to show a 50% reduction in the rate of oral corticosteroid use in the fluticasone group, assuming a 12.5% rate of use in the placebo group, an intraclass correlation of 10% for clustering of upper respiratory tract infections within individual children, and an average of 10 infections per child, at a two-sided alpha level of 5%. We analyzed all randomly assigned children according to the intention-to-treat principle, with children included in the analysis until the end of the follow-up period, whether or not the study drug was discontinued; children whose parents withdrew them from the study were included in the analysis until the last contact, without imputation of values for missing data. An independent data and safety monitoring board, whose members were unaware of the group assignments, reviewed all serious adverse events to ascertain whether the event was potentially related to the study drug, to unblind the data, if necessary, or to recommend withdrawal of the child from the study. There were no interim analyses, nor was there an a priori stopping rule.

We examined the treatment effect using generalized linear regression models with binomial, Poisson (with overdispersion), or normal distribution, as applicable. Differences in event rates based on numbers of upper respiratory tract infections were adjusted for the clustering of upper respiratory tract infections in individual children, and an offset variable was used to account for variations in person-time, when applicable.[34] Analyses of safety outcomes over the course of the study period were adjusted for baseline values and length of follow-up. For the primary outcome and safety end points, we repeated the analyses with adjustment for imbalances between the groups and for potential confounding variables (site, type of spacer, age, sex, race or ethnic group, birth weight, serum IgE level, presence or absence of eczema, presence or absence of a family history of asthma, presence or absence of exposure to tobacco in utero and in the household, status with respect to day-care attendance, age at first wheezing episode, number of times rescue systemic corticosteroids had been used in

the previous 12 months, duration of viral prodrome, vaccination status, season in which the upper respiratory tract infection occurred, and duration of follow-up). In per-protocol analyses, we censored the data at the time of the discontinuation of the study drug.

The models were selected with the use of the stepwise selection method and Akaike's Information Criterion. The number needed to treat or harm was derived from the odds ratio with the use of Visual Rx (www.nntonline.net).[35,36] Twenty-one analyses were fully prespecified, and the following seven analyses were post hoc: percentages of children with acute care visits, use of rescue corticosteroids, and hospitalization; bone age; severity of symptoms during episodes treated with or without systemic corticosteroids; correlation between cumulative dose and the primary and safety outcomes; and number needed to harm. Harm was defined as failure to thrive, which in turn was defined by a weight below the 3rd percentile (z score, less than –2) at the end of the study period or a decrease in weight by at least two major percentile lines on the Centers for Disease Control and Prevention growth charts (change in z score, less than –1.28).[31,37]

Continuous values are expressed as means ±SD or medians with interquartile ranges. All tests were two-sided, and estimates are shown with 95% confidence intervals. Analyses were performed with the use of SAS software, version 9.1 (SAS Institute). P values of less than 0.05 were considered to indicate statistical significance, with no correction for multiple testing.

RESULTS

CHILDREN

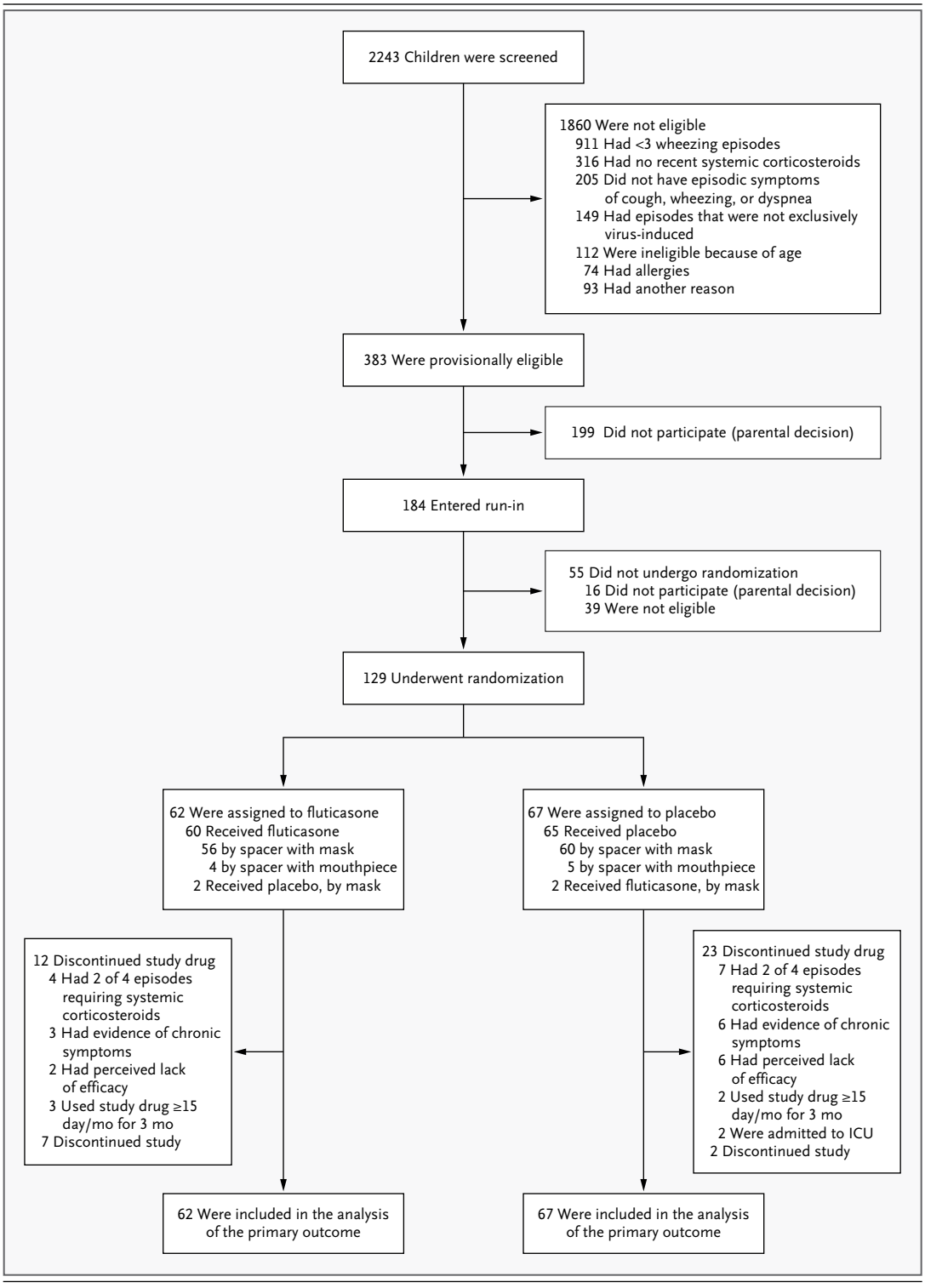
From November 1999 through April 2005, we screened 2243 children; 1860 (83%) were ineligible (Fig. 2). Of the 383 provisionally eligible children, the parents of 199 (52%) declined participation, and 184 children were enrolled. The children whose parents declined participation were similar to those who were enrolled with respect to age, sex, and family income (with postal code used as a surrogate for family income). A total of 129 children were randomly assigned to a study group — 62 to the fluticasone group and 67 to the placebo group. The study drug was prematurely discontinued in 35 children (12 in the fluticasone group and 23 in the placebo group); 9 children (7 in the fluticasone group and 2 in the placebo group) were lost to follow-up, with no significant difference between the groups in overall withdrawals (P=0.54). The baseline characteristics of the two groups were similar, except that there were more boys, and the children were older at the time of the first wheezing episode, in the placebo group (Table 1). There were no significant differences between the groups in the number of upper respiratory tract infections, the duration of treatment and follow-up periods, or the blinding of the treatment assignment, which was maintained in every case (Table E1 and Figure E1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

PRIMARY OUTCOME

Eight percent of upper respiratory tract infections in the fluticasone group led to treatment with rescue systemic corticosteroids, as compared with 18% of those in the placebo group (odds ratio, 0.49; 95% confidence interval [CI], 0.30 to 0.83) (Table 2). The odds ratio was similar with the per-protocol analysis, in which data were censored at the time of discontinuation of the study drug (odds ratio, 0.42; 95% CI, 0.25 to 0.73), and after adjustment for sex (odds ratio, 0.54; 95% CI, 0.32 to 0.91). As compared with children receiving placebo, significantly fewer children receiving fluticasone were treated with one or more bursts of systemic corticosteroids during the trial (39% vs. 64%; risk ratio with fluticasone, 0.60; 95% CI, 0.43 to 0.87) (Fig. E1 in the Supplementary Appendix). A post hoc analysis confirmed that symptom scores (calculated on the basis of a 17-item diary in which each item is ranked on a 7-point Likert scale, with higher scores indicating greater intensity of symptoms) were higher for episodes in which children were treated with systemic corticosteroids than for those in which children were not treated with systemic corticosteroids (197 [interquartile range, 95 to 332] vs. 36 [interquartile range, 12 to 86], P<0.001]. The numbers needed to treat to prevent systemic corticosteroid use were 4 children (95% CI, 3 to 13) and 13 upper respiratory tract infections (95% CI, 9 to 39).

SECONDARY OUTCOMES

The proportion of upper respiratory tract infections that were associated with symptoms of dyspnea, wheezing or cough, acute care visits, and hospital admissions for these symptoms did not



differ significantly between the groups (Table 2). In 56% of acute care visits, no albuterol treatment was given; a post hoc analysis showed that children in the fluticasone group had fewer visits involving two or more albuterol treatments than did children in the placebo group (26% vs. 42%, $P=0.03$). Children treated with fluticasone had a shorter duration of symptoms and of use of β_2-agonists during the course of the upper respiratory tract infections than those who were given

Figure 2 (facing page). Screening, Randomization, Follow-up, and Analysis.

Of the 184 children who entered the run-in phase, 55 did not undergo randomization: 16 did not participate (parental decision) and 39 were ineligible owing to evidence of chronic symptoms (12 children), no documentation of recent systemic corticosteroid use (9), allergy (8), or other reasons (10). Of the 129 children who were randomly assigned to one of the two groups, most (88%) qualified after a single run-in period; 16 children had an upper respiratory tract infection, with the result that two run-in periods were needed for 15 children and three were needed for 1 child. Most children (94% in the fluticasone group and 93% in the placebo group) received a holding chamber with a mask. Two children in each group did not receive the assigned study drug but instead received the other study drug, owing to technical difficulties with centralized assignment procedures; the data for these children were analyzed according to the study drug they received. Two children in the fluticasone group and three in the placebo group in whom the study drug was prematurely discontinued also discontinued follow-up. The study agent (fluticasone or placebo) was used for at least one upper respiratory tract infection in all children who underwent randomization, and data on the primary outcome were thus available for all these children.

placebo. These observations remained valid when the analysis was restricted to upper respiratory tract infections that were treated without systemic corticosteroids (rate ratio for symptoms, 0.85; 95% CI, 0.73 to 0.99; rate ratio for albuterol, 0.85; 95% CI, 0.72 to 1.00). The negative effect on the parents' lives, whether reported as a global assessment or as a quality-of-life score, was smaller with fluticasone than with placebo (mean global assessment, 3 vs. 3.5; mean quality of life score, 5.77 vs. 5.23). At the termination of the trial, physicians recommended rescue albuterol as the sole treatment during subsequent episodes in 75% and 60% of children in the fluticasone and placebo groups, respectively (P=0.07).

SAFETY PROFILE

The distribution of height and weight at baseline and at the end of the study period is shown in Table E2 in the Supplementary Appendix. The gain in height and weight was significantly lower in children treated with fluticasone than in children given placebo (Table 3), with a difference between the groups of 5 percentage points. Neither the per-protocol analyses nor the analyses adjusted for covariates (presence or absence of a family history of asthma and presence or absence of exposure to tobacco in the household) showed a significant difference between the groups in height (difference in the z-score change from baseline, −0.08; 95% CI, −0.25 to 0.08 in per-protocol analysis; −0.16; 95% CI, −0.31 to 0.00 in analysis adjusted for covariates). The observed difference in weight between the groups was similar in the per-protocol and intention-to-treat analyses. Figure E2 in the Supplementary Appendix shows the distribution of the change from baseline in height and weight. Post hoc analyses showed a significant correlation between the cumulative dose of fluticasone and the change in height (r=−0.21, P=0.02), but not in weight (r=−0.11, P=0.21). Two children in the fluticasone group and one in the placebo group met the definition of failure to thrive; the number needed to harm (54 children) was not significant (P=0.61).[36] Owing to movement artifacts, only 59 children had valid bone mineral density measurements at both baseline and the end of the study period. There were no significant group differences in the change in lumbar bone mineral density, bone mineral content, or bone age; adjustment for covariates and per-protocol analyses did not alter these associations. Low values (less than −2 SD) for bone mineral density, bone mineral content, or basal cortisol level were infrequent in both groups, and all the children in whom low cortisol values were found had normal values when these tests were repeated or when corticotropin testing was performed.

ADVERSE EVENTS

Thirteen serious adverse events (four in the fluticasone group and nine in the placebo group) occurred in 13 children during the study period — namely, pneumonia (three events in the fluticasone group and two in the placebo group), seizure (one event in each group), admission to an intensive care unit (two in the placebo group), burn (one in the placebo group), respiratory syncytial virus infection (one in the placebo group), atelectasis (one in the placebo group), and Kawasaki's disease (one in the placebo group). None of the serious adverse events were considered by an independent physician masked to treatment assignment to be attributable to the study drug. The distribution of nonserious adverse events was similar between the groups (Table E3 in the Supplementary Appendix).

DISCUSSION

In this proof-of-concept trial, high-dose fluticasone administered preemptively at the onset of up-

Table 1. Characteristics of the Participants at Baseline.*

Variable	Fluticasone Group (N=62)	Placebo Group (N=67)
Demographic characteristics		
Age — yr	2.60±1.09	2.86±1.20
Male sex — no. (%)	32 (52)	46 (69)
Race or ethnic group — no. (%)†		
White	50 (81)	50 (75)
Black	4 (6)	3 (4)
Other	8 (13)	14 (21)
Risk factors		
Birth at <37 wk gestation — no. (%)	5 (8)	3 (4)
Birth weight <2500 g — no. (%)	4 (6)	4 (6)
Food or drug allergy — no. (%)	6 (10)	8 (12)
Itchy rash for at least 6 months, ever — no. (%)‡	9 (15)	10 (15)
Eczema, ever — no. (%)§	21 (34)	34 (51)
Serum IgE ≥250 μg/liter — no./total no. (%)	9/56 (16)	13/62 (21)
Family history of asthma — no. (%)	31 (50)	29 (43)
Maternal asthma — no. (%)	12 (19)	12 (18)
Exposure to tobacco smoke — no. (%)		
In utero	11 (18)	9 (13)
In household	14 (23)	14 (21)
Day-care attendance — no. (%)	40 (65)	43 (64)
Illness before randomization		
Age at first wheezing episode — mo	10.8±8.6	12.6±9.1
≥1 hospital admission for wheezing ever — no. (%)	46 (74)	52 (78)
≥1 hospital admission in previous year — no. (%)	29 (47)	35 (52)
Courses of systemic corticosteroids in previous year — no.	2.3±1.1	2.4±1.4
Reported interval between onset of upper respiratory tract infection and wheezing — hr¶	31±19.8	36.5±23.7
Immunization status at randomization — no. (%)		
Pneumococcus	10 (16)	14 (21)
Influenza	17 (27)	16 (24)
Varicella	29 (47)	37 (55)
Preventive strategy before enrollment — no. (%)		
None	3 (5)	3 (4)
Antileukotriene agents	0	1 (1)
Maintenance inhaled corticosteroids	5 (8)	9 (13)
Episodic inhaled corticosteroids	54 (87)	54 (81)

* Plus–minus values are means ±SD.
† Race or ethnic group was determined by the research nurse or respiratory technician at the time of enrollment.
‡ A question from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire[25] was used to identify symptoms that were suggestive of eczema.
§ Eczema since birth was determined by parental report.
¶ Times are based on parents' reports of the usual interval between the onset of upper respiratory tract infections and the onset of wheezing for episodes occurring before randomization.

per respiratory tract infections reduced the frequency of clinician-initiated treatment with oral corticosteroids by 10 percentage points, a relative reduction of 50%. As compared with their counterparts who received placebo, children who were treated with fluticasone had symptoms that were milder and of shorter duration; they required fewer days of albuterol use, and their illness had a less negative effect on their parents' quality of life. There were no significant differences in the peak use of albuterol during upper respiratory tract infections, acute-care visits or hospitalizations for wheezing, or premature discontinuation of the study drug. The preemptive use of fluticasone was, however, associated with a reduced gain in height and weight. Because the adverse effects of preemptive treatment with fluticasone are still unknown, the potential risks associated with fluticasone treatment currently outweigh the identified benefit.

The duration of symptoms and of rescue β_2-agonist use was reduced by 10 to 15% (representing 1 to 2 days) in the fluticasone group as compared with the placebo group. The magnitude of the effect did not vary significantly whether it was assessed by means of oral report, diary, or dose counter. Similar benefits were observed in the case of exacerbations that did not require treatment with systemic corticosteroids, confirming that the effect also applied to mild exacerbations. As compared with placebo, the use of fluticasone had a smaller overall negative effect on parents and on their quality of life, although the latter difference was small.

The smaller gain in height and weight in children treated with fluticasone as compared with those given placebo is cause for concern. The magnitude of the effect on height was similar to that observed with 1-year treatment with daily low-dose fluticasone (200 μg) in preschool-age children.[38] The nonsignificant group difference observed after adjustment for covariates and in per-protocol analyses does not rule out a significant effect, particularly in view of the correlation between the cumulative dose and the change in height.[39] To our knowledge, weight loss has not been previously reported in patients treated with inhaled corticosteroids[40]; in fact, the opposite would be expected through a systemic effect. The power of our study to detect a clinically important difference (0.5 SD) in bone mineral density at an alpha level of 0.05 was only 73%. Moreover, the basal cortisol level is a relatively insensitive measure of adrenal dysfunction, and measurements at baseline and at the end of the study period would fail to identify a transient adrenal suppression during or immediately after preemptive treatment.[40] Whether trends toward more respiratory and gastrointestinal infections in the fluticasone-treated group are associated with the treatment or could be explained by small imbalances between the groups with respect to tobacco exposure and vaccination status is unclear.

The study results must be interpreted in light of the following limitations. First, we strived to enroll a homogeneous group of preschool-age children with a phenotype of virus-induced wheezing. Seventy-six percent of the children had normal serum IgE levels, a proportion similar to that previously reported among children with transient wheezing.[6] Despite our best intentions, we inadvertently included nine children (7% of randomly assigned children) in whom persistent or atopic asthma symptoms developed during the study period. Second, we were unable to identify characteristics of patients that could modulate the risk–benefit ratio for preemptive treatment. Third, we tested parents' initiation of preemptive treatment with fluticasone as it would happen in real-life practice. Because of the perceived importance of treatment early in the course of an upper respiratory tract infection, the intervention was based on parental perception of the presence of an upper respiratory tract infection, rather than on objective documentation of infection or a specified minimal duration of symptoms.[41] Although a viral cause has been confirmed in 74% of upper respiratory tract infections identified by parents,[42] we cannot rule out possible misidentification of colds. Fourth, the subjectivity involved in physicians' prescribing of systemic corticosteroids would tend to underestimate any true association, thus reinforcing the significance of our findings. The higher severity of episodes treated with systemic corticosteroids as compared with those treated without systemic corticosteroids would support the appropriateness of corticosteroid prescriptions. Finally, we empirically used 1500 μg of fluticasone per day in this proof-of-concept study; the minimal dose and duration of treatment required to achieve similar outcomes remain to be clarified.

The findings of this trial apply to a small group of carefully screened young children with

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Fluticasone Group (N=62)	Placebo Group (N=67)	Odds Ratio for Fluticasone Group (95% CI)	Rate Ratio for Fluticasone Group (95% CI)	Mean Difference between Fluticasone and Placebo Groups (95% CI)
Primary outcome					
No. of URTIs	521	526			
URTIs requiring courses of systemic corticosteroids — no. (%)	43 (8)	93 (18)	0.49 (0.30 to 0.83)		
Secondary outcomes					
Asthma exacerbations					
No. of URTIs	521	526			
URTIs with asthma symptoms — no. (%)†	466 (89)	488 (93)	0.64 (0.36 to 1.13)		
Use of health care services					
Acute care visits for asthma			0.79 (0.53 to 1.19)		
No. of URTIs	521	526			
No. of visits	107	146			
Hospital admissions for asthma			0.67 (0.29 to 1.38)		
No. of URTIs	521	526			
No. of admissions	11	18			
Children with ≥1 acute care visit for asthma — no. (%)	44 (71)	54 (81)	0.59 (0.26 to 1.33)		
Children with ≥1 course of systemic corticosteroids — no. (%)	24 (39)	43 (64)	0.35 (0.17 to 0.72)		
Children with ≥1 hospital admission for asthma — no. (%)	10 (16)	15 (22)	0.67 (0.27 to 1.62)		
Children who discontinued study drug prematurely — no. (%)	12 (19)	23 (34)	0.46 (0.20 to 1.03)		
Asthma symptoms					
Duration‡					
Oral report				0.82 (0.71 to 0.95)	
No. of URTIs	466	488			
Duration per URTI — days	5.66±4.37	6.88±5.13			
Diary report				0.85 (0.72 to 1.01)	
No. of URTIs	308	277			
Duration per URTI — median days (interquartile range)	4 (2 to 6.5)	5 (3 to 8)			
Intensity					
Diary report					−27.94 (−54.70 to −1.18)
No. of URTIs	308	277			
Average daily score per URTI — median (interquartile range)§	31 (10 to 77.5)	49 (16 to 117)			

Rescue β_2-agonist use			
Duration			
Oral report			0.80 (0.68 to 0.94)
No. of URTIs	433	451	
No. of days of use per URTI — median (interquartile range)	4 (2 to 7)	6 (3 to 9)	
Diary report			0.83 (0.73 to 0.94)
No. of URTIs	372	392	
No. of days of use per URTI — median (interquartile range)	6 (4 to 9)	7 (5 to 10)	
Dose counter			0.85 (0.74 to 0.98)
No. of URTIs	281	334	
No. of days of use per URTI — median (interquartile range)	5 (3 to 8)	6 (4 to 10)	
Intensity¶			
Diary report			0.83 (0.64 to 1.08)
No. of URTIs	372	392	
Sum of daily puffs per URTI — median (interquartile range)	19 (6 to 46)	23.5 (8 to 54)	
Dose counter — sum of daily puffs			0.80 (0.68 to 0.94)
No. of URTIs	281	334	
Sum of daily puffs per URTI — median (interquartile range)	36 (23 to 61)	44 (25 to 78)	
Peak daily use¶			
Oral report			0.95 (0.84 to 1.08)
No. of URTIs	431	449	
Puffs per day — median (interquartile range)	8 (4 to 12)	8 (6 to 13)	
Diary report			0.92 (0.76 to 1.10)
No. of URTIs	372	392	
Puffs per day — median (interquartile range)	8 (4 to 13)	8 (4 to 13)	
Dose counter			0.92 (0.79 to 1.06)
No. of URTIs	281	334	
Puffs per day — median (interquartile range)	12 (8 to 18)	12 (8 to 18)	

Table 2. (Continued.)

Outcome	Fluticasone Group (N=62)	Placebo Group (N=67)	Odds Ratio for Fluticasone Group (95% CI)	Rate Ratio for Fluticasone Group (95% CI)	Mean Difference between Fluticasone and Placebo Groups (95% CI)
Effect on parents during URTI					
Global assessment‖					−0.70 (−1.19 to −0.20)
No. of URTIs	347	332			
Score — median (interquartile range)	3 (1 to 4)	3.5 (2 to 5)			
Quality of life**					0.49 (0.10 to 0.89)
No. of URTIs	419	403			
Score — median (interquartile range)	5.77 (4.54 to 6.62)	5.23 (4.00 to 6.31)			
Work day or activity day missed				0.75 (0.45 to 1.26)	
No. of URTIs	335	325			
No. of days missed — median (interquartile range)	0 (0 to 1)	0 (0 to 1)			

* Plus–minus values are means ±SD. Unless otherwise specified, all summary estimates (odds ratio, rate ratio, and mean difference) are from the intention-to-treat analysis, with adjustment for the clustering of upper respiratory tract infections (URTIs) in individual children and an offset variable to account for variations in person-time, when applicable. A URTI was considered to have occurred when parents reported it at monthly contacts or in diaries.

† A URTI with asthma symptoms was considered to be a URTI that included at least 1 day with one or more symptoms of cough, wheezing, or dyspnea as reported by parents at the monthly contact. Data on URTIs with incomplete reports were excluded.

‡ The duration of symptoms is the number of days with one or more symptoms of cough, wheezing, or dyspnea as reported by parents on the monthly contact or diary. Data on URTIs with incomplete reports and diaries were excluded.

§ Average daily scores were calculated from a 17-item diary (best total score, 17; worst total score, 119) completed daily from the beginning until the end of symptoms. Each item was rated on a 7-point Likert scale (minimum score for intensity, 1; maximum score, 7). Two items pertained to cough, two items to wheezing, four items to dyspnea, one item to night awakenings, five items to general well-being, and three items to the child's response to albuterol inhalations. The diary was developed for this trial with the use of a standardized procedure (item generation, item reduction, and item presentation and scaling).[27] Data on URTIs with missing or incomplete diaries were excluded.

¶ Intensity refers to the cumulative number of inhalations and highest number (peak) of daily inhalations per URTI as recorded in monthly contacts, diaries, and dose counters. For the few days when the number of puffs exceeded 24 per day, we imputed the average of the values recorded the day before and the day after the outlier day, on the assumption that the large number of puffs on the outlier days was due to unintentional activation of the dose counter (e.g., during transport). All albuterol doses received during acute care visits and hospital admissions were added to the diary and dose counters, with the use of the following conversion factor: 1.25 mg of nebulized albuterol = 3 inhalations of 100 μg of albuterol. Data on URTIs for which there was missing or incomplete monthly contact or diary information, or for which dose counters did not function properly, were excluded.

‖ The global assessment of the effect of the child's flare-up on the parents was based on their response at the end of the episode to the question, "Overall, how much did this asthma flare-up affect you?" Responses ranged from 1 ("not at all") to 7 ("extremely").

** Quality of life was assessed by the average score on the 13-item Paediatric Asthma Caregiver's Quality of Life Questionnaire developed by Juniper et al. (in which the score for each item ranges from 1 to 7, with higher scores indicating better quality of life),[28] modified to cover the duration of the URTI. A value of 0.5 on a 7-point Likert scale indicates a minimally important group difference.[28,29]

Table 3. Secondary Outcomes Pertaining to the Safety Profile.*

Outcome	Fluticasone Group			Placebo Group			Group Difference (95% CI)†	
	Baseline	End Point	Change from Baseline‡	Baseline	End Point	Change from Baseline‡	Intention-to-Treat Analysis	Per-Protocol Analysis
Height								
No. of children	62	58	58	66	62	62		
Measurement — cm§	91.38±9.63	97.98±9.10	6.23±2.62	93.66±10.09	99.94±9.38	6.56±2.90	−0.61 (−1.31 to 0.09)	−0.22 (−0.90 to 0.46)
z score¶	0.28±0.87	0.12±0.93	−0.19±0.42	0.34±1.13	0.34±1.11	0.00±0.48	−0.24 (−0.40 to −0.08)	−0.08 (−0.25 to 0.08)
z score less than −2 — no. (%)¶	1 (2)	1 (2)	—	2 (3)	1 (2)	—		
Weight								
No. of children	62	59	59	67	64	64		
Measurement — kg§	14.25±3.03	15.94±3.23	1.53±1.17	15.24±4.67	17.34±6.11	2.17±1.79	−0.71 (−1.19 to −0.24)	−0.55 (−1.01 to −0.09)
z score¶	0.40±1.11	0.29±1.12	−0.15±0.48	0.49±1.18	0.60±1.26	0.11±0.43	−0.26 (−0.41 to −0.09)	−0.18 (−0.34 to −0.03)
z score less than −2 — no. (%)¶	1 (2)	2 (3)	—	1 (1)	1 (2)	—		
Bone mineral density								
No. of children	32	41	27	43	48	32		
z score¶	0.03±1.15	−0.23±1.01	−0.19±0.75	−0.005±1.27	−0.14±1.20	−0.32±0.70	0.08 (−0.26 to 0.44)	0.10 (−0.58 to 0.77)
z score less than −2 — no. (%)¶	2 (6)	1 (2)	—	1 (2)	2 (4)	—		
Bone mineral content								
No. of children	32	41	27	43	48	32		
Measurement — g	7.83±2.28	9.06±2.52	1.54±1.23	8.08±2.49	9.13±2.31	1.49±0.90	−0.01 (−0.51 to 0.49)	−0.08 (−0.94 to 0.79)
Bone age								
No. of children	32	41	27	43	48	32		
Measurement — mo	30.31±13.02	38.05±12.15	9.36±6.09	30.71±12.28	40.12±14.66	9.66±6.39	−0.75 (−3.50 to 1.99)	−0.48 (−4.68 to 3.72)
Basal cortisol‖								
No. of children	58	48		64	51			
z score less than −2 — no. (%)	0	1 (2)	—	2 (3)	2 (4)	—		

* Values are means ±SD, with the standard deviation estimated from the regression model.

† The group difference is the change in the fluticasone group as compared with that in the placebo group. Group differences, adjusted for baseline values and duration of follow-up, are shown for the intention-to-treat analysis (which included data until the end of the study period) and the per-protocol analysis (in which data were censored at the time of study-drug discontinuation, if applicable).

‡ The change from baseline was calculated on the basis of the number of children with valid measurements at both the beginning and end of the study period; owing to movement artifacts, changes in bone mineral density, bone mineral content, and bone age were calculated on the basis of 27 children in the fluticasone group and 32 in the placebo group.

§ These are raw values, not adjusted for sex and not annualized. We caution readers in the interpretation of these values that do not take into account any group difference in sex and age.

¶ Values were adjusted for age and sex, on the basis of pediatric reference values for height and weight[31] and for bone mineral density.[30] Adjusted values are depicted as z scores, representing the standard-deviation units from the expected mean of zero. A change from baseline of zero indicates that children followed the expected gain (or growth curve) from baseline until the end of the study period. Positive z-score values represent a higher gain than expected, and negative values, a smaller gain than expected. A change from the baseline z score that was greater than 0.5 SD was considered a priori to be indicative of a clinically important difference.

‖ The basal cortisol level was measured in a serum sample obtained before 8 a.m. Values below −2 SD represent values that are less than 138 nmol per liter (5.0 μg per deciliter)[33]; all of the children with abnormal values either had normal values when the tests were repeated (for values between 100 and 137 nmol per liter [between 3.62 and 4.99 μg per deciliter]) or had a normal response to corticotropin testing (for values below 100 nmol per liter).

frequent wheezing episodes triggered by upper respiratory tract infections, no intercurrent symptoms or suspected allergy, and recent moderate or severe episodes. Only 17% of the children we screened met our selection criteria. Most participants (83%) were 1 to 3 years of age; in the preceding year they had received, on average, two courses of systemic corticosteroids, and half the children had been hospitalized. The findings should not be generalized to older children or to children with aeroallergen sensitization, owing to their specific exclusion from this study. In summary, preemptive fluticasone treatment, as compared with placebo, was associated with fewer wheezing episodes treated with systemic corticosteroids, but the smaller gain in height and weight and the potential unknown adverse effects are cause for concern and indicate that this management strategy should not yet be recommended for use in clinical practice.

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