Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma

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Background: Outcome data are needed to base recommendations for controller asthma medication use in school-aged children.

Objective: We sought to determine intraindividual and interindividual response profiles and predictors of response to an inhaled corticosteroid (ICS) and a leukotriene receptor antagonist (LTRA).

Methods: An ICS, fluticasone propionate (100 μg twice daily), and an LTRA, montelukast (5-10 mg nightly, age dependent), were administered to children ages 6 to 17 years with mild-to-moderate persistent asthma using only as-needed bronchodilators in a multicenter, double-masked, 2-sequence, 16-week crossover trial. Clinical, pulmonary, and inflammatory responses to these controllers were evaluated.

Results: Improvements in most clinical asthma control measures occurred with both controllers. However, clinical outcomes (asthma control days [ACDs], the validated Asthma Control Questionnaire, and albuterol use), pulmonary responses (FEV_1/forced vital capacity, peak expiratory flow variability, morning peak expiratory flow, and measures of impedance), and inflammatory biomarkers (exhaled nitric oxide [eNO]) improved significantly more with fluticasone than with montelukast treatment. eNO was both a predictor of ACDs ($P = .011$) and a response indicator ($P = .003$) in

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*See Appendix E1 in the Online Repository of this article at www.jacionline.org for members of the Childhood Asthma Research and Education (CARE) Network involved in this study. The members of the Writing Committee were R. Zeiger (Chair), S. Szefler, B. Phillips, V. Chinchilli, R. Lemanske, F. Martinez, R. Strunk, M. Schatz, and G. Larsen.

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discriminating the difference in ACD response between fluticasone and montelukast.
Conclusions: The more favorable clinical, pulmonary, and inflammatory responses to an ICS than to an LTRA provide pediatric-based group evidence to support ICSs as the preferred first-line therapy for mild-to-moderate persistent asthma in children. eNO, as a predictor of response, might help to identify individual children not receiving controller medication who achieve a greater improvement in ACDs with an ICS compared with an LTRA. (J Allergy Clin Immunol 2006;117:45-52.)

Key words: *Asthma control days, asthma control outcomes, Asthma Control Questionnaire, exhaled nitric oxide, fluticasone propionate, inhaled corticosteroids, leukotriene receptor antagonists, montelukast, pulmonary response*

Abbreviations used
ACD: Asthma control day
ACQ: Asthma Control Questionnaire
AX: Area of reactance
CARE: Childhood Asthma Research and Education Network
eNO: Exhaled nitric oxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist
NHLBI: National Heart, Lung, and Blood Institute
PC_{20}: Methacholine dose required to reduce baseline FEV_1 by 20%
PEF: Peak expiratory flow
R5: Resistance of the respiratory system at 5 Hz

Guidelines recommend controller treatment for persistent asthma in both children and adults[1,2]; however, a recent worldwide survey reported that anti-inflammatory preventative medication use in such patients fell far short of their goal, reaching no higher than 26% in any of the 5 regions studied.[3] The Childhood Asthma Management Program demonstrated that long-term treatment with inhaled corticosteroids (ICSs) was both safe and superior to either nedocromil or placebo in reducing asthma burden in children with mild-to-moderate persistent asthma.[4] These findings served as the strongest evidence to support ICSs as first-line therapy for persistent asthma in children. Since the Childhood Asthma Management Program trial, leukotriene receptor antagonists (LTRAs) were introduced as effective controller therapy compared with placebo for persistent childhood[5] and adult[6] asthma. In adults meta-analyses of studies comparing ICSs with LTRAs as monotherapy for mild-to-moderate persistent asthma demonstrated the superiority of ICSs for most clinical, pulmonary, and use outcomes.[7,8] However, caution is needed in applying these results to children because the 3 pediatric trials in the above meta-analyses were uninformative.[9,10] As such, trials were recommended to compare ICSs and LTRAs as monotherapy in pediatric asthma.[7]

In children with mild-to-moderate asthma, a recent 2-sequence, 16-week, crossover National Heart, Lung, and Blood Institute (NHLBI) Childhood Asthma Research and Education (CARE) Network trial characterized within-subject FEV_1 responses to fluticasone versus montelukast.[11] This trial reported that the subgroup of children with lower pulmonary function or higher levels of biomarkers associated with allergic inflammation showed better lung function responses to ICSs.[11] It should be remembered that pulmonary function responses to controller therapy generally correlate poorly with many nonpulmonary clinical control outcomes.[12] As such, we now report additional outcomes comparing monotherapy ICSs with LTRAs in asthma control in the aforementioned CARE Network trial. We find across all outcomes of asthma control a consistent and significant response favoring ICS treatment.

METHODS

Study design and analyses have been detailed previously and will only be summarized briefly.[11,13] One hundred forty-four children (ages 6-17 years) with mild-to-moderate persistent asthma fulfilling the following characteristics entered the randomized trial: (1) absence of corticosteroid therapy within 4 weeks, leukotriene modifier agents within 2 weeks, and respiratory tract infection within 4 weeks of enrollment; (2) asthma symptoms or rescue bronchodilator use on average of 3 or more days/week for 4 weeks before enrollment; (3) 12% or greater FEV_1 reversibility after maximum bronchodilation or methacholine dose required to reduce baseline FEV_1 by 20% (methacholine $PC_{20} \leq 12.5$ mg/mL); and (4) FEV_1 of 70% of predicted value or greater.[13] After approval by each center's institutional review board, informed consent was given by a parent-guardian, and assent was given verbally by children less than age 7 years and in writing by older children.

Study design

A 5- to 10-day run-in period after enrollment characterized the asthmatic features of the cohort while off controller therapy. The study was a multicenter, double-blind, randomized, 2-sequence, 16-week crossover trial stratified by clinical center, age, and FEV_1 (percent predicted) that compared head to head an ICS and a LTRA.[11] The ICS was fluticasone propionate (Flovent Diskus; GlaxoSmithKline, Research Triangle Park, NC; 100 μg per inhalation) administered as one inhalation twice daily and the LTRA was montelukast (Singulair; Merck and Co, West Point, Pa) taken as 1 tablet at night either as a 5-mg chewable tablet for those 6 to 14 years of age or as a 10-mg tablet for those 15 to 18 years of age.[11,13] During each 8-week treatment period, a participant received an active drug and a matching placebo for the alternative drug. On the basis of prior evidence,[14-16] the first 4 weeks of the second treatment period was deemed an adequate period for washout of study medication used in the first period of each treatment sequence. The second 4 weeks of each treatment period was used to compare outcomes between fluticasone and montelukast. Adherence as determined by means of Diskus dose indicator count and by means of tablet count or an eDEM Electronic Drug Exposure Monitor (AARDEX, Zug, Switzerland) was in excess of 85% for both and was comparable during both treatment periods.[11]

Outcome measures

The following outcomes were determined from entries on daily diaries. Asthma control days (ACDs), the principal secondary trial

outcome, was defined as a day with no daytime or nighttime asthma symptoms, no rescue albuterol for asthma symptoms or peak flow less than 80% of personal best, no asthma health care use, and no asthma-related absences from school or work.[11] Albuterol use for symptoms or peak expiratory flow (PEF) of less than 80% of personal best was recorded as puffs per day and derived from the daily diaries. PEF was determined on awakening and before bedtime by using electronic peak flow measurements (AM1; Jaeger, Hoechberg, Germany).[11] Percentage peak flow variability was determined by dividing the difference in morning and evening PEF by the evening PEF and multiplying by 100.

The following outcomes were determined at randomization and at each treatment visit. The 7-item validated Asthma Control Questionnaire (ACQ), used with author permission,[17] consists of 3 domains (symptoms, albuterol use, and FEV_1) scored on a 7-point scale (0 = good control, 6 = poor control). At randomization and at each 4-week visit, the ACQ was completed by a parent-guardian with participant assistance or by the adolescent after recalling symptoms and albuterol use over the previous week. FEV_1 was recorded at the visit and scored on the questionnaire. Lower ACQ scores indicate better asthma control. An improvement in asthma control with treatment would be indicated by a decrease in the ACQ score.

Exhaled nitric oxide (eNO) was measured with the NIOX system (Aerocrine AB, Stockholm, Sweden) by using standardized procedures.[13,18]

FEV_1 and FEV_1/forced vital capacity (FVC) were determined by means of spirometry,[13] which was performed at least 4 hours after the last use of a short-acting bronchodilator.[19]

Resistance of the respiratory system at 5 Hz (R5) and area of reactance (AX) were determined by means of impulse oscillometry measurement of impedance, as potential indicators of small airway function, with the Jaeger Masterscreen IO System (VIASYS Healthcare GmbH, Hoechberg, Germany). Impulse oscillometry was performed by using standard methods before spirometry, with at least 3 separate measurements being obtained.[20,21] It assesses respiratory system impedance and allows calculation of the contribution of resistance and reactance to the total respiratory system. The AX value is an integrated response index for reactance reflecting the integral of the negative values of reactance from 5 Hz to the resonant frequency, the frequency at which reactance is zero.[20]

Characterization procedures

The following procedures were performed before randomization, as described previously, to help characterize the participants' asthma phenotype[11,13]: asthma history, allergen skin tests, blood total eosinophil count, serum eosinophil cationic protein measurement, serum total IgE measurement, urinary leukotriene E_4 measurement, spirometry, maximum postbronchodilator spirometry, methacholine PC_{20}, impulse oscillometry, and eNO measurement.

Statistical analyses

The target sample size was 140 randomized children in this 2×2 crossover design. This sample size provided 90% statistical power with a 2-sided .05 significance level test while allowing for as much as 15% withdrawals for detecting that the Kendall correlation coefficient exceeds 0.2 in absolute value with respect to the primary outcome of FEV_1 response to the 2 treatment regimens. With respect to the secondary statistical analyses explored here, including ACDs, the target sample size of 140 randomized children provided a 95% CI with end points of ± 0.15 for a Pearson-type correlation when the true correlation is 0.5 or greater and there is a maximum of a 15% dropout rate.

A placebo washout period between treatment sequences was not implemented at the request of 2 institutional review boards. Previous studies have indicated that the first 4 weeks of the second treatment period was a sufficient time for study medication washout.[14-16] As such, the first 4 weeks of each treatment period served as pseudo-washout periods and were not included in the statistical analyses. The second 4 weeks of each treatment period were used to compare responses to treatments. Analyses were adjusted for the small period and sequence effects of the crossover design. Because the study was not designed with the intention to conduct an intent-to-treat analysis, only participants who completed both treatment periods were included in the analyses.

For clinical measurements determined on the basis of diary card entries, averages over the entire last 4 weeks of each treatment period were used. For outcome responses, a mixed-effects, generalized linear model was applied to account for period and sequence effects (variations in responses across period and sequence that are not related to the treatment) within the repeated measurements feature of the crossover design. Restricted maximum likelihood estimation was applied to estimate all of the model parameters by using the PROC MIXED function of SAS 8.2 (SAS Institute, Inc, Cary, NC). The outcome values were corrected in further analyses for small sequence effects and small-to-moderate period effects for each of the 2 treatments. Statistically significant period effects were observed for ACD (-0.26 days/week), morning PEF rate (-2.83 L/min), and eNO (4.36 ppb) responses for each of the 2 treatments, indicating that patients improved slightly over time for these outcomes regardless of treatment.

Kendall correlation coefficients assessed the relationships among clinical, pulmonary, and eNO responses to fluticasone and montelukast and differences between fluticasone and montelukast treatments. The concordance correlation coefficient, which is suited for the measurement of agreement beyond a simple linear relationship, describes the relationship between montelukast and fluticasone ACD responses.[22] The continuous responses to fluticasone and montelukast were examined separately and as a difference (fluticasone response minus montelukast response). There was no center effect for any of the outcomes explored. Potential predictors included baseline asthma characteristics, pulmonary function, and biomarkers. Base-2 logarithmic transformation was used for several variables (PC_{20} and the biomarkers because of skewed distributions).[11] ACD responses were calculated as an average across the last 4 weeks of the treatment period, and the difference from baseline mimics a continuous response. Therefore the ACD responses were analyzed by using linear regression analyses with a stepwise selection process through the PROC REG function of SAS 8.2. Graphic displays of the results used Microsoft PowerPoint 2000 and SPLUS 2000.

RESULTS

Study cohort

The study design, cohort enrollment, and retention schemata and baseline characteristics have been reported previously.[11,13] One hundred twenty-seven (88.2%) of the 144 participants completed both treatment arms and are included in the present report. They had features consistent with mild-to-moderate persistent asthma, and demographics were 48% minority, 41% female, and 33% between 6 and 9 years of age.[11]

Asthma control outcomes

Clinical. ACDs were significantly increased both by fluticasone (2.8 days/week [SE 0.23]) and montelukast (2.1 days/week [SE 0.23]), with a concordance correlation of 0.70 (95% CI, 0.60-0.78) between the 2 treatments. ACDs were significantly higher for fluticasone than for montelukast (P value for difference $< .001$, Table I). The

TABLE I. Asthma control responses to fluticasone and montelukast and differences between treatments (fluticasone minus montelukast) adjusted for period and sequence effects

		Effects			Difference	
Outcome variable	No. of subjects	Baseline mean (95% CI)	Adjusted* FP mean (95% CI)	Adjusted* Mt mean (95% CI)	Difference (FP − Mt)† (95% CI)	*P* value
Clinical measurements						
Average no. of ACDs (d/wk)	123	2.2 (1.9 to 2.5)	5.0 (4.6 to 5.4)¶	4.3 (3.9 to 4.8)¶	0.7 (0.4 to 1.0)	<.0001
ACQ overall score (units)	127	0.96 (0.89 to 1.03)	0.59 (0.50 to 0.69)¶	0.76 (0.66 to 0.87)‖	−0.17 (−0.27 to −0.07)	.0009
Albuterol use (no. of puffs/wk)	120	7.5 (6.4 to 8.6)	3.1 (1.9 to 4.2)¶	4.4 (3.1 to 5.6)¶	−1.3 (−2.4 to −0.1)	.0305
Pulmonary measurements (prebronchodilator)						
FEV_1/FVC (%)	126	80.1 (79.1 to 81.1)	82.2 (80.9 to 83.6)¶	79.0 (77.6 to 80.5)‡	3.2 (2.3 to 4.1)	<.0001
Peak flow variability (%)	126	9.3 (8.6 to 10.0)	7.5 (6.9 to 8.1)§	8.5 (7.5 to 9.5)	−1.0 (−1.9 to −0.1)	.0301
Morning PEF (L/min)	126	307.6 (293.7 to 321.6)	334.2 (313.3 to 355.1)¶	324.8 (304.3 to 345.3)¶	9.4 (4.6 to 14.2)	.0002
R5 (kPa/L/s)	123	0.64 (0.61 to 0.67)	0.60 (0.56 to 0.63)‡	0.63 (0.59 to 0.67)	−0.03 (−0.05 to −0.01)	.0027
AX (kPa/L)	122	1.60 (1.42 to 1.77)	1.25 (1.06 to 1.43)§	1.53 (1.33 to 1.73)‡	−0.29 (−0.43 to −0.14)	.0003
Biomarker measurement						
eNO (ppb)	99	39.5 (34.2 to 44.7)	20.6 (15.0 to 26.2)¶	30.9 (25.5 to 36.2)‖	−10.3 (−16.9 to −3.7)	.0028

*Adjusted for period and sequence effects.
†Significant negative values for differences between fluticasone minus montelukast for ACQ score, albuterol use, PEF variability, R5, AX, and eNO level indicate improvement in outcome favoring fluticasone.
‡$P < .05$, §$P < .01$, ‖$P < .001$, and ¶$P < .0001$ for changes from baseline by treatments (FEV_1/FVC, R5, and AX as percentage changes from baseline and the other measures as differences from baseline).

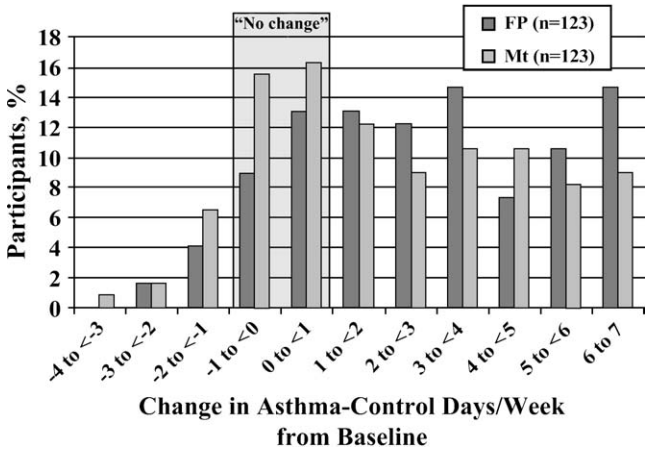

FIG 1. Changes in ACDs by treatment group. A range from +1 to −1 day/week is classified as indicating no change in ACDs. *FP,* Fluticasone propionate; *Mt,* montelukast.

distribution of ACDs by treatment group is depicted in Fig 1. For fluticasone, 13% improved 1 to less than 2 days/week and 59% improved 2 days/week or more, and for montelukast, 12% improved 1 to less than 2 days/week and 47% improved 2 days/week or more. When comparing responses within individuals, 29.3% of participants achieved at least 1 more ACD per week during treatment with fluticasone than during treatment with montelukast, whereas only 12.2% achieved at least 1 more ACD per week during treatment with montelukast than during treatment with fluticasone (Fig 2). The participants who had more than 1-day improvement on fluticasone or montelukast were balanced in terms of sequence and period.

In addition, compared with baseline scores, both fluticasone and montelukast treatments were associated with significant improvements in ACQ scores, but better control was achieved with fluticasone ($P = .0009$, Table I). Finally, although albuterol use decreased significantly with both treatments, a greater decrease occurred with fluticasone ($P = .031$, Table I).

Pulmonary function. Fluticasone treatment led to significant improvements in prebronchodilator FEV_1/FVC,

PEF variability, morning PEF, R5, and AX (Table I), in addition to the previous report of a 6.8% mean improvement in FEV_1.[11] After montelukast treatment, significant pulmonary improvements from baseline were noted in morning PEF (Table I) and, as reported previously, a 1.9% improvement in FEV_1.[11] However, montelukast treatment was associated with a significant but small decrease in prebronchodilator FEV_1/FVC ($P = .033$, Table I). Greater improvements in prebronchodilator FEV_1/FVC ($P < .0001$), PEF variability ($P = .030$), morning PEF ($P = .0002$), R5 ($P = .003$), and AX ($P = .0003$) occurred after fluticasone than after montelukast treatment (Table I).

eNO. eNO decreased after both fluticasone and montelukast treatments ($P < .0001$), but the decrease was greater after fluticasone ($P = .0028$, Table I).

Baseline predictors of outcomes by and between treatments

At baseline, higher eNO levels ($P = .036$), greater albuterol use ($P = .029$), and more positive aeroallergen skin test responses ($P = .008$), in addition to fewer ACDs ($P < .0001$), significantly predicted more ACDs after fluticasone treatment by using univariate regression analysis (Table II). For montelukast, no predictor except fewer ACDs at baseline ($P < .0001$) was associated with more ACDs during treatment. Higher eNO levels at baseline was the only baseline characteristic that discriminated ACD response to treatments and was positively associated with greater ACD responses to fluticasone than to montelukast ($P = .011$, Table II).

Associations of eNO response to other responses

During treatment with fluticasone, decreases in eNO levels correlated with improvements in clinical responses (increases in ACDs [$r = -0.21$, $P < .01$], lower ACQ scores [$r = 0.26$, $P < .001$], and decreases in albuterol use [$r = 0.31$, $P < .0001$]) and greater pulmonary function (decreases in PEF variability [$r = 0.24$, $P < .001$] and increases in both morning PEF [$r = -0.19$, $P < .01$] and FEV_1/FVC [$r = -0.21$, $P < .01$]; Table III). During treatment with montelukast, decreases in eNO levels were only correlated with improvements in ACQ scores and albuterol use ($r = 0.18$ and 0.17, respectively; $P < .05$; Table III). No relationships were observed between eNO response and changes in impedance after treatments with either fluticasone or montelukast (Table III).

DISCUSSION

National[1] and international[2] guidelines recommend ICSs compared with LTRAs as the preferred drugs for both children and adults with mild-to-moderate persistent asthma on the basis of evidence from trials in adults.[7,8] Given the lack of definitive comparative evidence in children, the NHLBI CARE Network conducted a crossover trial that both characterized and compared responses to these 2 controllers. Szefler et al[11] recently reported the primary FEV_1 outcome data of this trial. They noted a significant concordance in FEV_1 responses between the 2 medications. However, they found significantly more participants had a meaningful increase in FEV_1 of at least 7.5% to an ICS than a LTRA. Intraindividual analyses revealed that lower levels of pulmonary function, greater bronchodilator use, and higher levels of biomarkers of inflammation, including eNO, at baseline related to a better differential pulmonary response to fluticasone compared with montelukast.[11]

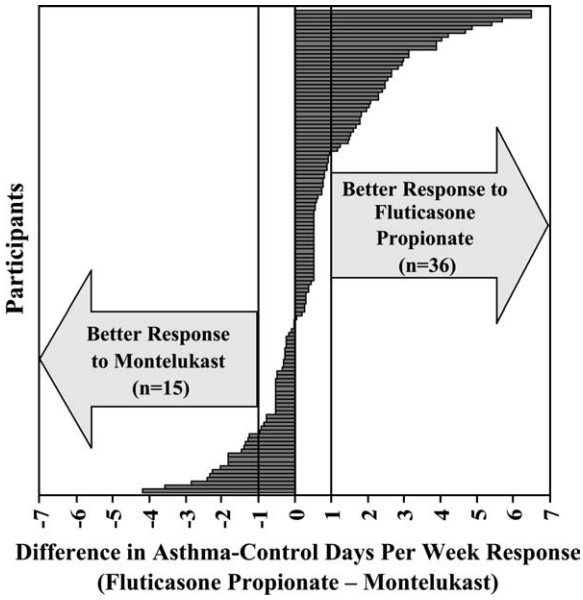

FIG 2. Difference in ACDs between fluticasone propionate and montelukast (fluticasone minus montelukast) for individual participants. Each *line* designates a single participant.

Given the heterogeneity and variability of asthma, multiple response outcomes are needed before a comprehensive comparison can be made between asthma controllers.[23] In this light the present report extends the findings of Szefler et al[11] to several other measures of asthma control, including ACDs. Both fluticasone and montelukast led to significant improvements in many measures of asthma control. However, similar to our earlier report,[11] we found strong evidence of greater mean improvements after 8 weeks of therapy with an ICS compared with a LTRA across many other outcomes (ACDs, ACQ score, albuterol use, eNO, PEF variability, morning PEF, and measures of impedance; Table I), although there is some redundancy of information in these correlated outcomes. The improved impedance measurements with ICS treatment were manifested by decreased absolute respiratory system resistance (Table I) and a diminished AX, potential indicators of improved small airway function.[20,21] Our findings are generally consistent with the results of the Montelukast Study in Asthma in Children, a 1-year trial in 6- to 14-years-olds with mild persistent asthma, that reported that for most asthma control outcomes, fluticasone was superior to montelukast.[24] Similarly, in a 3-month, parallel-group, double-blind, placebo-controlled study in a cohort of children with more severe asthma

TABLE II. Linear regression analyses for continuous ACD response (treatment minus baseline) for fluticasone propionate and montelukast and the difference between the 2 medications (fluticasone minus montelukast) for each baseline predictor adjusted for period and sequence effects

Baseline predictor	Outcome variable	Parameter estimate	SE	*P* value
Bronchodilator use per week: For each unit increase in bronchodilator use at baseline, the FP response is increased by 0.06 ACDs/wk on average (5 additional puffs per week of albuterol at baseline increases the response to FP by 0.30 ACDs/wk on average).	ACD difference, FP	0.06	0.03	.029
	ACD difference, Mt	0.02	0.03	.431
	Difference (FP − Mt)	0.04	0.02	.065
ACDs per week: For each decrease in ACDs per week at baseline, the FP and Mt responses are increased by 0.56 and 0.51 ACDs/wk on average, respectively.	ACD difference, FP	−0.56	0.08	<.0001
	ACD difference, Mt	−0.51	0.09	<.0001
	Difference (FP − Mt)	−0.06	0.07	.445
eNO (ppb)*: For each doubling of eNO at baseline, the FP response increases by 0.37 ACDs/wk on average. Additionally, for each doubling of eNO at baseline, the difference in response (FP − Mt) is increased by 0.31 ACDs/wk on average.	ACD difference, FP	0.37	0.17	.036
	ACD difference, Mt	0.06	0.17	.747
	Difference (FP − Mt)	0.31	0.12	.011
No. of positive aeroallergen skin test responses (maximum = 8): For each additional positive skin test response, the FP response increases by 0.27 ACDs/wk on average.	ACD difference, FP	0.27	0.10	.008
	ACD difference, Mt	0.15	0.10	.159
	Difference (FP − Mt)	0.12	0.08	.106

The following baseline characteristics did not significantly ($P > .05$) relate to ACD response differences for fluticasone, montelukast, or fluticasone minus montelukast: prebronchodilator FEV_1 percent predicted, prebronchodilator FEV_1/FVC (percentage), maximum bronchodilator response, PC_{20}, blood total eosinophil count, eosinophilic cationic protein level, serum IgE level, urinary leukotriene E_4 level, age, age at onset of asthma, duration of asthma, sex, ethnicity or body mass.

FP, Fluticasone propionate; *Mt*, montelukast.

*Analyzed by using a Log_2 transformation.

TABLE III. Kendall correlations (± 95% CIs) between changes in eNO levels and various clinical and pulmonary outcome responses to fluticasone and montelukast treatments adjusted for period and sequence effects

eNO vs outcome measures	Fluticasone	Montelukast
ACDs (d/wk)	−0.21† (−0.33 to −0.08)	−0.04 (−0.17 to 0.09)
ACQ (score)	0.26‡ (0.13 to 0.40)	0.17* (0.06 to 0.29)
Albuterol use (puffs/d)	0.31§ (0.20 to 0.43)	0.17* (0.04 to 0.31)
PEF variability (%)	0.24‡ (0.12 to 0.36)	0.12 (−0.00 to 0.24)
Morning PEF (L/min)	−0.19† (−0.32 to −0.05)	−0.10 (−0.23 to 0.03)
FEV_1 (L)	−0.11 (−0.25 to 0.02)	0.08 (−0.07 to 0.23)
FEV_1/FVC (ratio)	−0.21† (−0.33 to −0.09)	−0.05 (−0.20 to 0.09)
R5 (kPa/L/s)	−0.01 (−0.14 to 0.13)	0.02 (−0.12 to 0.15)
AX (kPa/L)	0.03 (−0.10 to 0.17)	−0.02 (−0.17 to 0.13)

As eNO levels decrease with treatment, indicating reduced inflammation, ACDs, morning PEF, and FEV_1/FVC increase, indicating improvement with treatment, and ACQ scores, albuterol use, and PEF variability decrease, indicating also improvements with treatments.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

§$P \leq .0001$.

(mean FEV_1 percent predicted of about 76%) than our cohort (FEV_1 percent predicted of 95%),[13] fluticasone was significantly more effective than montelukast in improving pulmonary function, asthma symptoms, and rescue albuterol use.[25] Detailed analyses of ACDs revealed a moderate concordance in response to both the ICS and the LTRA (Fig 1), as was seen for the FEV_1 response to these medications noted previously.[11] Similar to the FEV_1 response, mean ACDs were greater after ICS than LTRA treatment (Table I), and at least 2-fold more children experienced at least 1 more ACD after treatment with an ICS compared with when they were treated with a LTRA (Fig 2). Moreover, increased baseline levels of eNO favored a greater differential ACD response to an ICS than to an LTRA (Table II). These findings are consistent with our prior report that showed that increased baseline levels of biomarkers of inflammation, including eNO, predicted a better differential FEV_1 response to an ICS than to a LTRA.[11]

Determinants of ACD response to fluticasone and montelukast were assessed separately. A greater ACD response to ICSs is associated with baseline levels of less

ACDs, greater albuterol use, more positive skin test responses, and higher eNO levels (Table II). These findings are consistent with those of a recent clinical trial of adolescents and adults with mild persistent asthma that reported that more days per week of albuterol use was associated with a significantly better rescue-free day response to an ICS compared with a LTRA.[26] In addition, increased baseline eNO levels have also been shown in our initial report in children[11] and in a recent trial in adults[27] to predict better FEV_1 responses to ICSs, an outcome that poorly correlates with ACDs.[28] No baseline patient characteristic except for baseline severity of the clinical outcome (ie, less ACDs) significantly related to an increase in ACD response with montelukast treatment (Table II). These findings corroborate studies that also failed to identify patient characteristics predictive of response to montelukast treatment for outcomes similar to ACDs: days without asthma in 2- to 5-year-old children,[29] total daily as-needed β-agonist use in children 6 to 14 years of age,[5] and daytime symptoms in adults.[30]

eNO, a biomarker for airway inflammation,[31,32] was reduced significantly more with an ICS (48% reduction) than with a LTRA (28% reduction, Table I), findings previously reported in smaller comparative monotherapy studies in children[33] and adults.[34,35] The reductions in eNO levels in our trial are of similar magnitude to reductions in eNO levels with ICSs[36,37] and LTRAs[38] in steroid-naive school-aged children with persistent asthma reported earlier in smaller studies.[39] We also showed that the eNO response to controller treatment, particularly ICSs, reflects overall asthma control, as seen by the association we found between the decrease in eNO levels and improvement in many asthma clinical and pulmonary control measures (Table III). Taken together, our findings suggest that eNO levels in steroid-naive mild-to-moderate persistent asthma in childhood might predict both greater ACD (Table II) and FEV_1[11] responses to an ICS than a LTRA (Table II), and its decrease with treatment might be a response indicator of asthma control, as shown here (Table III) and by others.[40,41]

The present crossover design has the advantage over the parallel design with respect to assessing individual performance because a participant partakes in both treatment regimens. In a parallel design it is not possible to compare treatments within each individual; only group-based comparisons are possible. It is for this reason that our study was able to show that baseline levels of eNO discriminated within participants a better ACD response to an ICS than a LTRA. These findings emphasize the advantage of studying and reporting data based on individual patient responses to better individualize asthma treatment strategies rather than rely solely on group mean data. The major disadvantage with a crossover design is whether carryover effects lead to a statistical bias. This concern usually is diminished by the incorporation of an appropriate washout period between treatment administrations. For ethical reasons, however, our trial did not include a placebo washout period because 2 of the local institutional review boards would not approve of an untreated placebo period in children with persistent asthma. Therefore we did not use the data from the first 4 weeks of each treatment period because the first 4 weeks of the second treatment period functioned as a surrogate washout period. Previous studies have indicated that the first 4-week interval of the second treatment period was a sufficient time for washout of fluticasone or montelukast.[14-16]

The trial's major limitation is the absence of a placebo arm that would have helped adjust for the day-to-day fluctuation in asthma and the hard-to-quantify benefit provided by trial participation. The absence of a placebo group imparts some uncertainly in analyzing more subjective outcomes, such as symptoms (a component in ACDs and ACQ scores). However, it is unlikely that the absence of a placebo group affects the fundamental nature of our findings because more favorable responses with ICS treatment than with LTRA treatment were found across outcomes, both those with subjective components (ACDs and ACQ scores) and those that are objective (pulmonary function and eNO level). These short-term findings need to be confirmed in more long-term studies that address both the variability of asthma over time and through different seasons.

In summary, asthma control, assessed by use of several clinical, pulmonary, and inflammatory responses, improved consistently and significantly more with an ICS than a LTRA in children with mild-to-moderate persistent asthma, each treated with both controllers. These findings and those previously reported regarding mean group comparisons of responses to an ICS and a LTRA[11,24,25] provide pediatric-based evidence to support the present national and international recommendations for ICSs as the preferred first-line controller therapy for mild-to-moderate persistent childhood asthma. eNO, as a predictor of clinical and pulmonary responses, might be a useful marker to identify individual children solely receiving as-needed bronchodilators who achieve a greater improvement in ACDs (present study) and FEV_1[11] with an ICS compared with a LTRA.

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