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Can a Single Dose Response Predict the Effect of Montelukast on Exercise-Induced Bronchoconstriction?

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Summary. Rationale: Exercise-induced bronchoconstriction (EIB) can be prevented by a single dose of montelukast (MLK). The effect is variable, similar to the variable responsiveness observed after daily treatment with MLK. We hypothesized that the effect of a single MLK-dose (5 or 10 mg) on EIB could predict the clinical effectiveness of longer term once daily treatment. Methods: This was a prospective, open-label study. Twenty-four asthmatic adolescents (12–17 years) suboptimally controlled by low-dose inhaled corticosteroids, with $\geq$10% post-exercise fall in FEV_1, were included. They performed an exercise test at baseline, 20 hr after a single MLK-dose and 40–44 hr after the last dose of 4 weeks once daily treatment. The correlations between the effect of a single dose and 4 weeks treatment on area under the curve (AUC) and maximum % fall in FEV_1 were calculated. Results: $AUC_{0-20\,min}$ decreased significantly after a single MLK-dose ($P=0.001$, CI: 64.9–218.2), but not after 4 weeks of treatment ($P=0.080$, CI: −12.2 to 200.4). There was a moderate correlation between the effect of a single MLK-dose and 4 weeks treatment on $AUC_{0-20\,min}$, $r=0.49$ ($P=0.011$), and maximum % fall in FEV_1, $r=0.40$ ($P=0.035$). Conclusion: The protection provided by a single MLK-dose against EIB only modestly predicts the effect of regular treatment against EIB in adolescent asthmatics on low-dose inhaled corticosteroids. If used on a daily base, MLK offered clinically significant protection against EIB in two thirds of adolescents suboptimally controlled by low-dose ICS. **Pediatr Pulmonol. 2016;51:470–477.**

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INTRODUCTION

Asthma is a heterogeneous disease, which is reflected in the variability of individual patients' responses to medications. Symptomatic asthmatic children on low-dose inhaled corticosteroids (ICS) show a considerable variability in response to the currently available step-up options: that is, doubling the dose of ICS, adding a long-acting β2-agonist (LABA) or adding a leukotriene receptor antagonist (LTRA).[1] There is little evidence to guide clinicians to the most effective step-up option.

Adding an LTRA to ICS to reinforce anti-inflammatory treatment is one of the step-up options in children with persistent asthma symptoms.[2] Cysteinyl leukotrienes

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The study was performed at the Medisch Spectrum Twente, Enschede, the Netherlands.

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(CysLTs) are pro-inflammatory mediators causing potent and long-lasting airway narrowing. In exercise-induced bronchoconstriction (EIB), CysLTs are released from activated mast cells as a result of airway drying and cooling.[3] Compared to placebo, daily treatment with the LTRA montelukast (MLK) significantly attenuated EIB, measured by post-exercise maximum % fall in FEV_1 and area under the FEV_1 curve (AUC), in adults[4] and in children[4–8] uncontrolled by low-dose ICS. In adult asthmatics, a single MLK-dose (10 mg) provides a rapid (1 hr post-dosing)[9,10] protection against post-exercise maximum % fall in FEV_1 compared to placebo. Other placebo-controlled studies in both adults[11,12] and children (aged 4–14 years)[13] showed a sustained protection 24 hr after a single MLK-dose (4, 5, or 10 mg). In these studies, the reduction in both maximum % fall in FEV_1 and $AUC_{0\text{-}60min}$ was similar at 2 and 24 hr post-dosing.[11–13]

However, MLK does not protect against EIB in all children and 20–40% of children are considered non-responders both after a single dose[13,14] and longer term daily treatment.[4,6,8,15,16]

It is not clear if a single MLK-dose response against EIB relates to the clinical effectiveness following longer term daily MLK-treatment within the same child. If both treatment responses are mediated through the same pathway, a single dose response should predict the longer term clinical effectiveness of step-up therapy with MLK. In the present study, we investigated the relationship between a single dose response to MLK (5 or 10 mg) against EIB and the effectiveness after 4 weeks once daily MLK-treatment against EIB in children with mild-to-moderate persistent asthma suboptimally controlled by low-dose ICS.

MATERIALS AND METHODS

Subjects

Children were recruited from the pediatric outpatient clinic of the Medisch Spectrum Twente, Enschede, the Netherlands. Children aged 12–17 years, with a clinical history of persistent asthma and EIB, partly or fully uncontrolled (based on guideline-derived symptom scores[2]) by low doses of ICS alone (stable daily dose of 100–400 μg of beclomethasone dipropionate or equipotent for >6 weeks), were screened by a standardized treadmill exercise challenge.[17] Children were included if a fall in FEV_1 ≥10% from baseline occurred.[17,18] Other inclusion criteria comprised the ability to perform reproducible pulmonary function tests and baseline $FEV_1 \geq 70\%$ of predicted.

Exclusion criteria included viral upper airway infections, other lower airway or cardiac co-morbidities, or hospitalization due to an asthma exacerbation in the month before inclusion. Furthermore, children were excluded for use of systemic corticosteroids, antihistamines, LTRA, or anticholinergics in 2 weeks prior to the study or other medication changes during the treatment period. Children were not allowed to use short-acting bronchodilators within 8 hr or long-acting bronchodilators within 24 hr prior to testing or to perform vigorous exercise within 8 hr prior to testing.

The study was approved by the Medical Ethics Committee, Medisch Spectrum Twente, Enschede. All children gave written assent and their parents gave written informed consent. The study was registered online in the NTR register as NTR2059.

Study Design

The study had a prospective, open-label design. During baseline visit, children performed an asthma control questionnaire (ACQ) and pediatric asthma quality of life questionnaire (PAQLQ). Children performed an exercise challenge with lung function measurements pre- and repeatedly up to 30 min post-challenge.

One week after the baseline visit, children were started on a therapeutic MLK-dose (5 or 10 mg QD, depending on their age) before bedtime. Twenty hours after the first dose (through of dosing interval), a second exercise challenge was performed. After 30 ± 4 days of treatment, a third exercise challenge was performed. Children received the last MLK-dose 40–44 hr prior to the third challenge to ensure that the "longer term" anti-inflammatory effect was measured and not the more acute antagonistic effect of a single dose. Children were asked to bring their medication strip to the third visit to allow compliance check.

Exercise Challenge

Exercise challenges were performed by running with nose clipped on a treadmill (Horizon® fitness Ti22, Cottage Grove, Wisconsin) with an incline of 10% using a standardized ATS protocol.[17] Exercise challenges in children have a good short-term repeatability with a mean difference in fall in FEV_1 −0.4%, 95%CI: ± 12% over 3 days.[19]

ABBREVIATIONS:

ACQ	Asthma control questionnaire
AUC	Area under the FEV_1 curve
CysLT	Cysteinyl leukotrienes
EIB	Exercise-induced bronchoconstriction
FEV_1	Forced expiratory volume in 1 sec
ICS	Inhaled corticosteroid
LABA	Long-acting beta2-agonist
LTRA	Leukotriene receptor antagonist
MLK	Montelukast
PAQLQ	Pediatric asthma quality of life questionnaire
SABA	Short-acting beta2-agonist

All exercise challenges were performed in the afternoon (between 1.30 and 5 p.m.). During exercise, children inhaled dry air with a temperature of 20–25°C and a humidity of 16 ppm. The running speed of the treadmill was increased to raise the heart rate to approximately 90% of the predicted maximum for a total duration of 6 min. Spirometry was performed with a calibrated Microloop® MK8 Spirometer (Micromedical, Quayside, United Kingdom) before exercise (baseline value) and 1, 3, 6, 9, 12, 15, and 20 min after exercise.

Twenty minutes after exercise, or earlier at request, children received 100 μg salbutamol and spirometry was performed at $t = 21$, 23, 25, and 30 min until FEV_1 had returned to ≥95% of baseline value. If FEV_1 had not recovered to ≥95% of baseline after 30 min, children received a second dose of 100 μg salbutamol.

Questionnaires

The ACQ and PAQLQ questionnaires were performed at the screening and third visit to the outpatient clinic by the research assistant. The scoring of the ACQ[20] and PAQLQ[21] was previously described elsewhere.

Statistical Analysis

Data consisted of three sets of pre-exercise and post-exercise FEV_1 values at pre-defined time points. EIB was expressed as total area under the curve from 0 to 20 min post-exercise ($AUC_{0–20\,min}$), calculated by a trapezoid rule, and post-exercise % fall in FEV_1 from baseline at each time point. The time to recovery to ≥95% of baseline FEV_1 was retained for analysis, and the percentage of children not recovered after 20 min was calculated. Children who received a dose of salbutamol before 20 min post-exercise were excluded from this analysis. If FEV_1 did not decrease below 95% of baseline, the time to recovery was assigned a value of zero.

As CysLTs produce a potent and longlasting bronchoconstrictor effect on airway smooth muscle, MLK was anticipated to mainly attenuate the duration of bronchoconstriction, measured by the AUC.[3] This was previously confirmed in several large adult studies demonstrating a greater reduction in post-exercise AUC than in the maximum post-exercise % fall in FEV_1 after regular treatment with MLK.[22–24] Hence, the primary end point was the correlation (reported as the intraclass correlation coefficient) between the change in $AUC_{0–20\,min}$ after a single MLK-dose and after 4 weeks MLK-treatment. Secondary end points were the correlation between change in maximum % fall in FEV_1 after a single MLK-dose and 4 weeks MLK-treatment and percentage protection against EIB (defined as % reduction in $AUC_{0–20\,min}$ and maximum% fall in FEV_1) provided by a single MLK-dose and 4 weeks MLK-treatment. Changes between screening, second and third visits in all outcome variables were analyzed with Students' paired *t*-test (for normally distributed variables) or Wilcoxon-signed rank test (for variables with a skewed distribution).

A cross-tabulation was made of responders and non-responders to a single MLK-dose and 4 weeks MLK-treatment, for response based on ≥25% reduction in maximum % fall in FEV_1 and on ≥25% reduction in $AUC_{0–20\,min}$ after MLK.

SPSS® 20.0 for Windows® was used for statistical analysis. A *P*-value of <0.05 was considered statistically significant. A sample size of 19 achieves 80% power to detect a difference of 0.60 between the null hypothesis correlation of 0.0 and the alternative hypothesis correlation of 0.60 using a two-sided hypothesis test with a significance level of 0.050.

RESULTS

Fifty-one children were screened by a standardized exercise challenge. Twenty-seven children had a <10% post-exercise fall in FEV_1 and were excluded. Twenty-four eligible children were included of whom 21 completed the study. Patient baseline characteristics are presented in Table 1. Two children dropped out, due to reasons unrelated to MLK-treatment. One girl was excluded because she underwent another medication change during the treatment period.

Three children reported adverse events during the treatment period with MLK. Two of them complained of headache during the first days of treatment, and one reported an increase in pre-existing symptoms of dizziness. All adverse events were mild and self-limiting.

All children included in this study were clinically suboptimally controlled on low-dose ICS and used short-

TABLE 1—Baseline Characteristics of Study Population (n = 24)

Male (%)	45.8
Age (years)	14.4 ± 1.6
Weight (kg)	55.8 ± 13.0
Height (cm)	167 ± 12.6
BMI (kg/m^2)	19.8 ± 3.1
Baseline FEV_1 (% predicted)	92.9 ± 12.4
Allergic (%)	86
RAST animal dander positive (%)	54
RAST house dust mite positive (%)	75
RAST tree pollen positive (%)	46
RAST grass pollen positive (%)	46
Nasal corticosteroid use (%)	50
ICS use (%)	100
ICS dose (μg)	200 (100–400)

Data expressed as mean ± SD, median (range), or percentage of total patients.

BMI, body mass index; FEV_1, forced expiratory volume in 1 sec; RAST, radio-allergosorbent test; LABA, long-acting beta2-agonist; SABA, short-acting beta2-agonist; ICS, inhaled corticosteroid.

TABLE 2— Analysis of End Points

End point	Baseline	Single dose	Difference (95%CI)	*P*-value	4 weeks	Difference (95%CI)	*P*-value
$AUC_{0-20\,min}$ (% min)	309.4 ± 221.3	167.9 ± 153.0	141.5 (64.9–218.2)	<0.05	215.3 ± 208.7	94.1 (−12.2–200.4)	0.08
Maximum fall in FEV_1 (%)	24.1 ± 13.4	18.3 ± 11.7	5.8 (2.4–9.2)	<0.05	19.7 ± 15.0	4.5 (−1.9 to 10.9)	0.16
Time to recovery to ≥95% of baseline (min)	21 (3–30)	12 (0–23)	9	<0.05	15 (0–21)	6	<0.05
Baseline FEV_1 (% predicted)	92.3 ± 11.9	92.5 ± 11.9	−0.2 (−2.9 to 2.5)	0.89	91.4 ± 12.6	0.9 (−1.9 to 3.8)	0.52
Weekly SABA use (puffs)	1.9 ± 1.8	n/a	n/a	n/a	1.6 ± 1.6	0.3 (−0.3 to 0.9)	0.27
ACQ score	1.07 ± 0.83	n/a	n/a	n/a	0.96 ± 0.73	0.11 (−0.25 to 0.46)	0.53
PAQLQ total	6.04 ± 0.98	n/a	n/a	n/a	6.34 ± 0.54	−0.31 (−0.71 to 0.09)	0.13
PAQLQ symptoms	5.82 ± 1.13	n/a	n/a	n/a	6.10 ± 0.72	−0.28 (−0.79 to 0.24)	0.28
PAQLQ activity limitation	5.66 ± 1.11	n/a	n/a	n/a	6.13 ± 0.66	−0.48 (−0.93 to −0.02)	<0.05
PAQLQ emotional function	6.54 ± 0.99	n/a	n/a	n/a	6.79 ± 0.54	−0.24 (−0.56 to 0.07)	0.13

Data expressed as mean ± SD or median (range), as appropriate.
$AUC_{0-20\,min}$, area under the curve 0–20 min post-exercise; FEV_1, forced expiratory volume in 1 sec; SABA, short-acting beta2-agonist; ACQ, asthma control questionnaire; PAQLQ, pediatric asthma quality of life questionnaire.

acting β2-agonists on an as-needed basis, with a self-reported mean (±SD) use of 1.9 (±1.8) puffs per week before the baseline exercise challenge and 1.6 (±1.6) puffs per week after 4 weeks of treatment with MLK. FEV_1 after a single MLK-dose and after 4 weeks treatment were not significantly different from FEV_1 before the baseline exercise challenge. All outcome variables are summarized in Table 2.

Exercise-Induced Bronchoconstriction Following MLK-Treatment

EIB, expressed as the $AUC_{0-20\,min}$, decreased significantly after a single MLK-dose ($P = 0.001$, CI: 64.9–218.2), but not after 4 weeks of treatment ($P = 0.080$, CI: −12.2 to 200.4) (Fig. 1). There was a moderate correlation between the response to a single MLK-dose and 4 weeks MLK-treatment on exercise-induced $AUC_{0-20\,min}$, $r = 0.49$ ($P = 0.011$) (Fig. 2A).

Exercise-induced maximum % fall in FEV_1 decreased significantly after a single MLK-dose ($P = 0.002$, CI: 2.4–9.2), but not after 4 weeks of MLK-treatment ($P = 0.16$, CI: −1.9 to 10.9). Mean % fall in FEV_1 (±SEM) at each time point post-exercise is shown in Figure 1 for all three exercise challenges. There was a weak correlation between the response to a single MLK-dose and to 4 weeks MLK-treatment on exercise-induced maximum % fall in FEV_1, $r = 0.40$ ($P = 0.035$) (Fig. 2B).

A single dose of MLK and 4 weeks MLK-treatment, respectively, provided 45.7 versus 30.4% reduction in $AUC_{0-20\,min}$ and 24.0% versus 18.5% reduction in maximum % fall in FEV_1.

When children with ≥25% reduction in maximum % fall in FEV_1 were considered responders to MLK, 10 out of 21 (48%) could be considered responders to MLK after a single MLK-dose, and an equal percentage after 4 weeks MLK treatment (Table 3). When children with ≥25% reduction in $AUC_{0-20\,min}$ were considered responders to MLK, 13 out of 21 (62%) could be considered responders after a single MLK-dose and 15 out of 21 (71%) after 4 weeks of MLK-treatment (Table 4).

Complete data sets for the evaluation of recovery were available for 18 children, as three children received a rescue gift of salbutamol before 20 min post-exercise (one child after the baseline exercise challenge, two children after the second challenge, and 2 children after the third challenge). After the screening exercise challenge, 35% of children recovered to ≥95% of baseline within 20 min; after a single MLK-dose and 4 weeks MLK-treatment, respectively, 68 and 72% of children recovered within 20 min. However, these differences were not statistically significant.

Quality of Life and Asthma Control

At the baseline visit, children had a mean ACQ score of 1.07 ± 0.83 units. Based on their ACQ, 10 out of 21

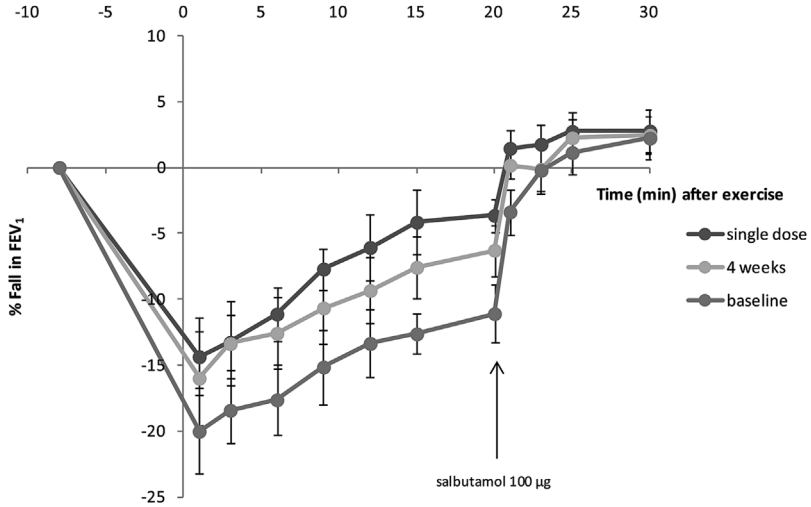

Fig. 1. Mean % fall in FEV_1 ($\pm$ SEM) at each time point post-exercise after a baseline exercise challenge, 20 hr after a single MLK-dose of 5 mg and 40–44 hr after the last dose of a 4 week course of MLK once daily.

children (48%) could be considered partly or fully uncontrolled (ACQ score ≥ 0.75), although all children were suboptimally controlled based on guideline derived symptom scores.[2] After 4 weeks MLK-treatment, there was no change in mean ACQ scores ($P = 0.53$, CI: -0.25 to 0.46) and 8 out of 21 children (38%) could still be considered partly or fully uncontrolled.

At baseline, quality of life was slightly impaired with a mean PAQLQ score of 6.04 ± 0.98 units. After 4 weeks MLK-treatment, there was no significant difference in total PAQLQ score ($P = 0.13$, CI: -0.71 to 0.09). However, there was a small, but significant improvement in the PAQLQ activity limitation domain score ($P = 0.040$, CI: -0.93 to -0.02).

DISCUSSION

In this study, we found a moderate correlation between the protective effect against EIB of a single MLK-dose and 4 weeks of MLK-treatment, expressed as post-exercise $AUC_{0–20\,min}$ and maximum % fall in FEV_1. A single MLK-dose provided a greater reduction in $AUC_{0–20\,min}$ post-exercise (45.7%) than 4 weeks of MLK-treatment (30.4%).

This was the first study that separated the single dose and longer term response to MLK by assessing EIB 20–24 hr after a single MLK-dose, and 40–44 hr after 4 weeks MLK-treatment, to measure their relationship. Previous studies both in adults[11,12] and children[13] showed a similar attenuation in EIB performed at the through interval (24 hr) after a single MLK-dose. Bronsky et al.[25] observed in adult asthmatics that this protective effect expired 32–36 hr after two once daily doses of MLK (2, 10, or 50 mg). However, Kim et al.[16] found a prolonged protective MLK-effect against EIB in asthmatic children, that is, 48 hr after the last dose of 8 weeks daily treatment, suggestive of anti-inflammatory properties of regular MLK-treatment. In an animal model of allergic asthma, it was shown that 4 weeks treatment with MLK has anti-inflammatory effects on the airway wall and lung parenchym.[26] In all other previous pediatric studies describing longer term protection against EIB, children performed an exercise challenge at the end of the dosing interval (i.e., 20–24 hr post-dosing),[5–7] which is expected to reflect the composite response to both the more acute, functional antagonistic, and the longer term, anti-inflammatory properties of MLK. By measuring EIB 40–44 hr after the last dose of 4 weeks of regular MLK-treatment, we allowed assessment of the anti-inflammatory MLK-effect only.

Our data can be affected by several factors. Firstly, the timing of the exercise challenges may have influenced our data. Based on pharmacological data showing a plasma half life of MLK of 2.7–5.5 hr, measuring the effect of a single MLK-dose 20–24 hr after dosing may underestimate the acute antagonistic effect of MLK. However, previous studies in both adults[11,12] and children (aged 4–14 years)[13] showed that the reduction in both maximum % fall in FEV_1 and $AUC_{0–60\,min}$ was similar at 2 and 24 hr after a single MLK-dose.[11–13]

The 40–44 hr time interval between the last dose of MLK and the exercise challenge can explain why we found a small reduction in AUC (30.5%) and maximum % fall in FEV_1 (18.5%) after 4 weeks of MLK-treatment. Previous pediatric studies reported 63.8% reduction in AUC[6] and 44.8–56.5% reduction in maximum % fall in FEV_1,[5–7] but measured the effect 10–24 hr after the last dose of 4 weeks treatment. However, the small effect of

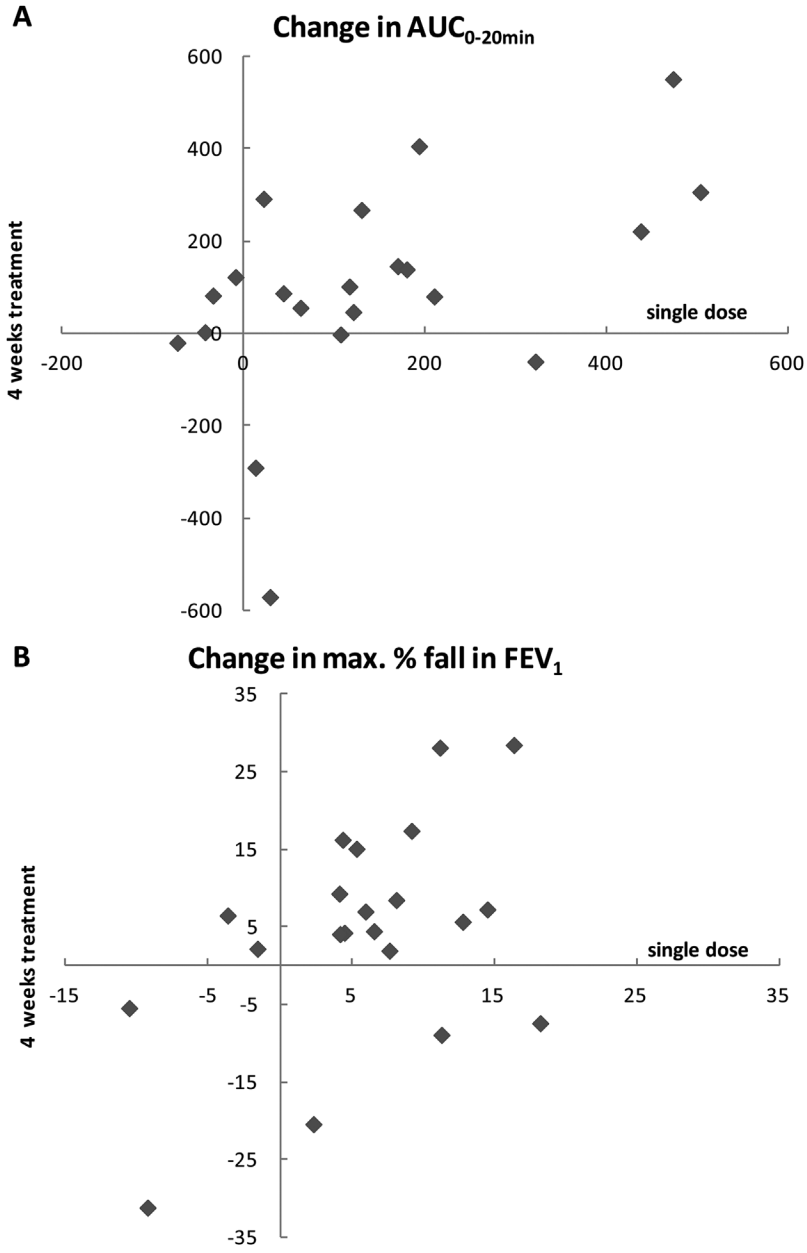

Fig. 2. Change in $AUC_{0-20\,min}$ (panel A) and maximum % fall in FEV_1 (panel B) between a baseline exercise challenge test (ECT) and an ECT after a single MLK-dose and between a baseline ECT and an ECT after 4 weeks MLK-treatment.

MLK on EIB after 4 weeks was consistent with the lack of effect on ACQ and PAQLQ scores. The treatment period of 4 weeks might have been rather short to evaluate the anti-inflammatory effects of MLK, but was similar to other pediatric studies describing the effect of regular daily MLK on EIB.[5–7]

A second possible confounder is the lack of a placebo arm. The difference in response after a single dose and 4 weeks MLK could result from variability in response to an exercise challenge. Repeatability of a field exercise challenge in children 8–11 years was −0.4% with a 95% CI of ±12%.[19] In the current study, the absolute difference in maximum % fall in FEV_1 between subsequent tests was <12% for most patients and, therefore, could be the result of test–retest variability. However, we performed our exercise challenge tests in standardized conditions minimizing climatic confounders.

A continuing effect of ICS treatment could have influenced the results after 4 weeks treatment, as we did not report the exact duration of ICS treatment before enrollment. The maximum effect of ICS on EIB is,

TABLE 3— Cross-Tabulation of the Response to Montelukast Based on ≥25% Reduction in Max. % Fall in FEV_1

	Response after 4 weeks treatment		
Response after single dose	Responder	Non-responder	Total
Responder	6	4	10
Non-responder	4	7	11
Total	10	11	21

A responder is defined as ≥25% reduction in post-exercise max. % fall in FEV_1 compared to baseline after respectively a single dose or 4 weeks montelukast.

TABLE 4— Cross-Tabulation of the Response to Montelukast Based on ≥25% Reduction in $AUC_{0–20\,min}$

	Response after 4 weeks treatment		
Response after single dose	Responder	Non-responder	Total
Responder	11	2	13
Non-responder	4	4	8
Total	15	6	21

A responder is defined as ≥25% reduction in $AUC_{0–20\,min}$ compared to baseline after respectively a single dose or 4 weeks montelukast.

however, attained within a few weeks.[27] Furthermore, three allergic patients were tested during the pollen season, which could have influenced their response to exercise.

A third factor that may have influenced our results is that based on ACQ scores both well controlled, as well as fully uncontrolled children were included. However, based on clinical symptoms, all children were partly or fully uncontrolled according to international guidelines. Furthermore, all children had ≥10% fall in FEV_1 at baseline, which is a sign of uncontrolled asthma. Subgroup analysis comparing children with ACQ scores <0.75 versus ≥0.75 did not show any significant differences.

Furthermore, children took MLK at home, unsupervised by hospital staff. However, we explicitly instructed the children and their parents about the timing of the medication gifts, and checked their compliance by checking their medication strip during study and following study completion. Asthmatic children in our outpatient clinic are reviewed for their adherence and inhalation technique every 3 months.

Interestingly, in our study a single dose provided a greater mean protection against EIB than 4 weeks treatment. However, some children reached a significant attenuation of EIB only after 4 weeks of treatment. Meanwhile, some patients only responded to a single MLK-dose and not to 4 weeks treatment. We speculate that this heterogeneity in response to a single MLK-dose and 4 weeks of MLK-treatment reflects the variable progression of airway inflammation and remodeling in children with asthma. When inflammation is relatively mild and EIB is mainly the result of transient increased airway smooth muscle tone due to mediator release, a single dose of MLK is effective and inflammation is easily reversible within 4 weeks treatment. However, when inflammation is more progressed and airway remodeling more pronounced, 4 weeks daily treatment is probably insufficient. In these patients, EIB might bounce back after the single-dose effect of MLK has waned.

Although MLK attenuated EIB, it provided no complete protection; an 18.3% maximum fall in FEV_1 after a single dose and a 19.7% fall after 4 weeks are still considered clinically relevant EIB. In real life, children using step-up treatment with MLK on a daily base will benefit from both the single-dose antagonistic effect and the anti-inflammatory effect of regular treatment. In our study, 7 (33%) children could be considered true non-responders with no response to either a single dose or 4 weeks treatment based on reduction in maximum % fall in FEV_1. Previous studies found similar or higher percentages of non-responders (ranging from 17.9 to 43%)[5,6,8,16,22–24] based on the reduction in % fall in FEV_1 after regular treatment with MLK. These studies used a variety of different cut-off values to differentiate between responders and non-responders. Some studies considered patients with ≥50%[5] reduction in maximum % fall in FEV_1 responders; others considered all patients with <10%,[6] <20%[8,16,23,24], or <30%[22] fall in FEV_1 responders.

When MLK response was defined based on reduction in AUC, only four (19%) children were considered non-responders. Previous large studies both in adults[22–24] and children[6] have shown that following exercise challenge MLK has a greater impact on AUC than on maximum % fall in FEV_1. For children practicing sports, the AUC, representing both the severity and duration of EIB, may be equally important as the maximum % fall in FEV_1.

In conclusion, in the present study, we found that the protection provided by a single dose of MLK against EIB only modestly predicts the effect of regular MLK-treatment against EIB. The single dose response to MLK was stronger than the response to 4 weeks regular treatment, implying that a high adherence is essential to profit from the full protective effect of MLK against EIB. If used on a daily base, MLK offered clinically significant protection against EIB in two-thirds of children sub-optimally controlled by low-dose ICS.

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