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Protocol

Adaptive clinical trial with pharmacokinetic-guided optimization of weight-based oral montelukast dose in children with acute asthma exacerbations

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ABSTRACT

Background: Children with acute asthma exacerbations are frequently hospitalized due to insufficient response to inhaled β-agonist and systemic corticosteroid treatments. Leukotriene (LT) mediated airway inflammation does not respond to these medications and contributes to insufficient clinical response that often necessitates hospitalization. Montelukast (MK) is a potent LT receptor antagonist, and IV MK caused rapid clinical improvement in adults with exacerbations, though the IV form is not FDA approved or currently available.
Methods: This is a phase 2, adaptive, double-masked RCT of high-dose oral MK, with escalating mg/kg dose levels informed by PK-guided modeling, added to standard treatment versus standard treatment alone, in children with exacerbations that are moderate or severe after initial treatment with inhaled albuterol. Study hypotheses are that- High-dose oral MK achieves peak plasma levels (C_{max})≥1,700 ng/ml in ≥86% of at least one of three sequential participant groups with escalating weight-based (mg/kg) doses between groups; participants randomized to high-dose oral MK have a 2 point or greater improvement of the validated acute asthma intensity research score (AAIRS) at 4 hours post-treatment in comparison with control group participants; and among MK recipients, C_{max} correlates with change of the AAIRS at 4 hours, after adjustment for pre-treatment exacerbation severity, respiratory viral detection, and systemic LT stress measured using plasma LTE_4.
Conclusions: This research will provide critical data for dosing and design decisions for a future randomized trial sufficiently powered to definitively determine efficacy in this population.
Trial Registration: NCT 05819541.

Keywords: Anti-asthmatic agents, Asthma, Glucocorticoids, Leukotriene E4, Leukotriene antagonist, Montelukast, Status asthmaticus

INTRODUCTION

Acute asthma exacerbations are a frequent reason for admission to children's hospitals with an alarming hospitalization rate (median 24%, range 13-50%).[1] Hospitalization is needed most often because the child does not respond sufficiently to inhaled β-agonist and systemic corticosteroid (CCS).[2-5]

Cysteinyl LTs are an important cause of CCS and β-agonist non-responsiveness.[6] LTs are inflammatory mediators synthesized by airway mast cells and eosinophils.[7-12] Synthesis is induced by viral respiratory infection and aeroallergens, the most frequent triggers of asthma exacerbations in children.[8,13]

Though some inflammatory pathways induced by these triggers are CCS-responsive, LT-mediated airway inflammation is not.[14-16] In addition, LTs cause potent bronchoconstriction that is not entirely β-agonist responsive.[6,7] A substantial proportion of hospitalizations for children presenting to U.S. EDs may be a result of LT-mediated inflammation not responsive to systemic CCS and inhaled β-agonist.

MK is a potent LT-receptor antagonist and FDA approved at a daily oral dose of 4-5 mg for chronic asthma and allergic rhinitis in children.[17] It is also a potent bronchodilator.[7,18,19] In two multi-site RCTs of adults with moderate and severe exacerbations and inadequate response to inhaled albuterol, intravenous (IV) MK caused rapid (within 10 minutes) and sustained improvement of lung function.[20,21] This was noted in all subjects, without selecting for CCS non-responsiveness, likely a result of some degree of LT-mediated inflammation in all participants. Regardless of mechanism, the broad response underscores the potential clinical impact of reducing LT-mediated airway inflammation during exacerbations in all patients. However, the standard 5 mg oral pediatric dose does not achieve peak plasma levels (C_{max}) comparable to the IV doses used in these RCTs, and IV MK is not FDA approved or commercially available.

Our preliminary pharmacokinetic (PK) study in 15 children with acute exacerbations demonstrated that 30 mg oral MK (mean 1.0 mg/kg) achieved C_{max}≥,700 ng/ml in 40% of participants, a C_{max} expected after IV doses used in the adult RCTs above.[22,23] Moreover, time to C_{max} was within the 4-hour window for hospitalization decision-making recommended by NHLBI guidelines.[24]

Study objectives and hypotheses

The first objective of this Phase 2 RCT is to determine whether escalating, weight-based doses of oral MK achieve peak C_{max} comparable to the IV preparation. Additional objectives are to determine whether these doses meaningfully decrease exacerbation severity and whether the degree of improvement is proportionate to C_{max}. We are testing three hypotheses: High-dose oral MK achieves C_{max} ≥1,700 ng/ml in ≥86% of at least one of three sequential participant groups with escalating weight-based (mg/kg) doses between groups. Participants randomized to high-dose oral MK have a 2 point or greater improvement of the validated AAIRS at 4 hours post-treatment in comparison with control group participants. Among MK recipients, C_{max} correlates with change of the AAIRS at 4 hours, after adjustment for pre-treatment exacerbation severity and systemic LT stress measured using urinary LTE_4.

Study rationale

LTs are an important cause of insufficient CCS and β-agonist response that results in hospitalization of children with acute asthma exacerbations.[2-5] High-dose oral MK may achieve C_{max} sufficient to mitigate airway inflammation and rapidly decrease exacerbation severity and need for hospitalization.

METHODS

Setting, study population and participant recruitment

We are conducting a Phase 2 RCT of high-dose oral MK or identical placebo, added to standard treatment in children aged 4-12 years with exacerbations that are moderate or severe after initial treatment with inhaled albuterol (Figure 1). The trial uses an adaptive dose-selection design in which interim PK analyses prospectively guide dose-escalation and mg/kg dose-level continuation decisions. Adaptations are limited to PK criteria (C_{max} relative to predefined exposure targets), and no efficacy data are used for adaptation. These prespecified rules determine whether subsequent participants receive the same or a higher weight-based dose of oral MK, consistent with regulatory definitions of adaptive dose-finding designs. Participants are recruited in the ED of the Monroe Carell Jr. Children's Hospital at Vanderbilt.

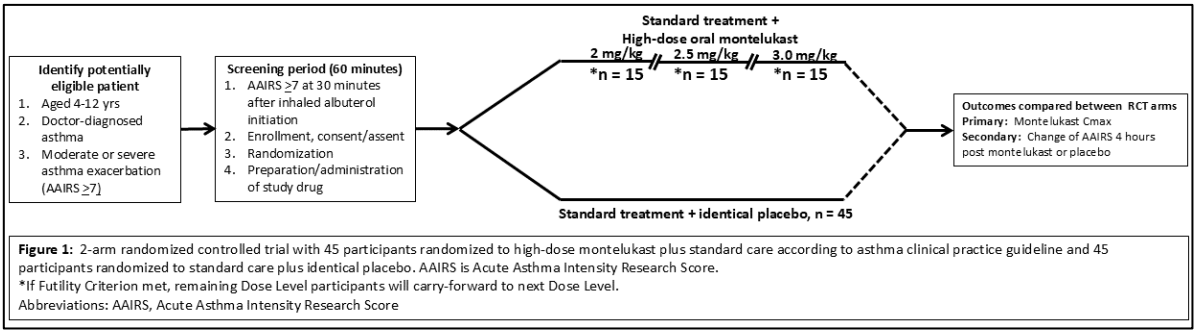


Figure 1: 2-arm randomized controlled trial with 45 participants randomized to high-dose montelukast plus standard care according to asthma clinical practice guideline and 45 participants randomized to standard care plus identical placebo. AAIRS is Acute Asthma Intensity Research Score.
*If Futility Criterion met, remaining Dose Level participants will carry-forward to next Dose Level.
Abbreviations: AAIRS, Acute Asthma Intensity Research Score

Figure 1: Overall randomized controlled trial design.

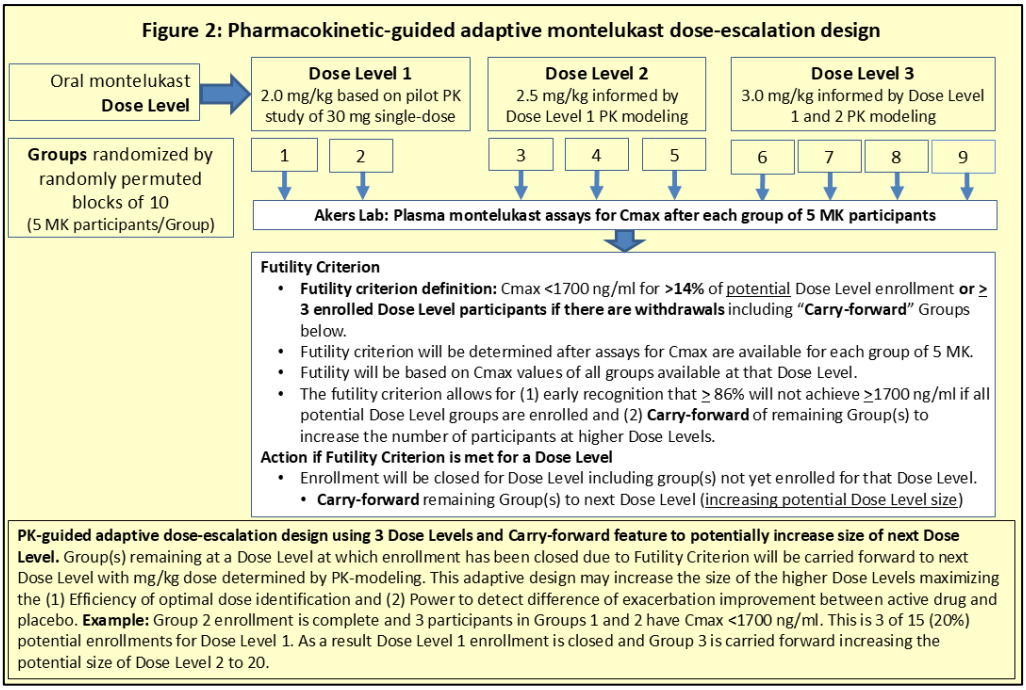


Figure 2: Pharmacokinetic guided adaptive ML dose-escalation design.

Clinical care for children with acute asthma exacerbations is motivated by a clinical practice guideline (CPG) developed using expert guidelines and best evidence.[24,25] The CPG has separate and interconnected sub-pathways for mild, moderate and severe exacerbations, defined using the validated (AAIRS, described below).[26]

Inclusion criteria include age 4-12 years, physician-diagnosed asthma, AAIRS ≥7 after at least 30 minutes of inhaled albuterol, and parent agreeing to phone follow-up 7-14 days after discharge. Exclusion criteria include gestational age <34 weeks, liver disease, allergy to MK, female with Tanner stage ≥2 breast development, gastroesophageal reflux requiring acid-blocking medication, or prior study enrollment. Exclusion criteria include history of anxiety disorder/other neuropsychiatric disorder except ADHD, score ≥25 on the 82-point screen for child anxiety related disorders (SCARED) questionnaire, or positive screen for suicide on the Columbia suicide severity rating scale (CSSR-S).[27,28]

Safety procedures

In 2020 the FDA applied a Boxed Warning for potential associations between daily MK use and neuropsychiatric events.[29] However, this decision was contrary to an FDA propensity-score based analyses of Sentinel Distributed Database data from 457,377 patients 6 years and older with asthma treated with MK versus inhaled CCS.[30] This analysis found no increased risk of any mental health outcome examined, including inpatient or outpatient depressive disorder, self-harm or suicide. Other investigators found no association between MK and neuropsychiatric events using the Sentinel Database and a large Swedish database.[31,32]

Using data from the National Poison Data System, we identified 17,069 single-drug MK ingestions of up to 445 mg in children aged 5-17 years in which single-drug exposure was ascertained and the lowest possible MK dose was accurately identified.[33] There were no serious events reported, with abdominal pain the most common side effect (0.23%). Among 618 ingestions of ≥50 mg (median 80 [IQR 60, 112] mg), there were again no serious events reported, with abdominal pain the most frequent (1.5%) side effect. Confusion was reported in 0.02% and hallucinations in 0.03% of the cohort of 17,069 but no neuropsychiatric events were reported in those with ingested doses ≥50 mg. The FDA granted an IND (#136451) for this research.

Safety procedures include screening for neuropsychiatric disorders using the SCARED parent questionnaire, a validated instrument to screen for childhood anxiety disorders, and the CSSR-S.[27,28] A positive response to either instrument is an exclusion criterion. Finally, when the participant is discharged and at 7-14 days we administer a side effect questionnaire based on those during placebo-controlled trials of daily MK and our study of MK overdoses.[17,33,34] Finally, blood is obtained for complete metabolic panels, including aspartate aminotransferase and alanine aminotransferase, before medication administration and up to 24 hours later.

Our institutional review board (IRB) has reviewed and approved the study protocol (IRB #230555). In addition, NHLBI Prevention of Pediatric Asthma (POPA) Data and Safety Monitoring Board (DSMB) performs independent monitoring of pharmacokinetic data and adverse events (AEs), oversees participant safety, and monitors the overall conduct of this clinical trial. The DSMB meets

with the study team twice yearly and on an ad hoc basis, reviews all AEs and PK data, and issues recommendations based on these reviews. Finally, a quarterly report of AEs is submitted for review to the FDA by the Principal Investigator (DHA).

Randomization and masking of treatment allocation

Participants are randomized in permuted blocks of randomly varying size, constrained so that each 10 participants include 5 MK and 5 placebo allocations (Figure 2). The randomization schedule was generated in R using custom code with a fixed random number seed for reproducibility[35] When the investigators place an Epic® order for drug, the randomization database communicates treatment allocation to the children's hospital pharmacy.

The clinical team, study personnel, and participant-parent dyad are masked to treatment allocation. The clinical team and participant are not provided study data to avoid influence on clinical decision-making.

Drug preparation and PK-guided adaptive dose-escalation

The pharmacy prepares MK sodium USP powder (PCCA, Houston, TX) as active drug in Ora-Blend suspending vehicle (Medisca, Montreal, CA) to a concentration of 10 mg/ml. Placebo is prepared as sucrose powder in Ora-Blend. Each preparation is transported to the bedside in an amber oral syringe (MK can be degraded by UV light). Study drug and placebo include a bar-coded label for scanned documentation and time stamp in Epic® and are administered orally followed by fruit juice or water to promote gastric absorption.

The study comprises three (2.0, 2.5, and 3.0 mg/kg, maximum 180 mg) sequentially escalating, weight-based MK dose levels. Dose level 1 (2.0 mg/kg) was based on our pilot study dose (1.0 mg/kg).[22] Dose levels 2 and 3 (2.5 and 3.0 mg/kg) were determined using linear modeling of pilot study data. These dose levels could be adjusted up or down based on computerized, PK-guided modeling of accrued PK data (Figure 1). Each dose level includes up to 3 groups of up to 10 participants each (5 randomized to MK) if there are no withdrawals.

If the C_{max} futility criterion (Figure 2) is met for a dose level after plasma MK assays are reported for a group, remaining groups for that Dose Level are moved to the next dose level (carry-forward feature). As noted above, this dose level can be adjusted based on PK-guided modeling of accrued PK data. This adaptive design enables accrued PK data to inform subsequent mg/kg doses and to increase the potential number of participants at subsequent dose levels, increasing statistical power and precision at higher mg/kg doses.

Among groups 1 and 2, 50% of participants failed to achieve the target C_{max}, and group 3 was moved to dose level 2. Among groups 3, 4, and 5, there were 27% failures, with group 6 moved to dose level 3. Among 10 MK recipients to date in Dose level 3 there are no failures to reach target C_{max} levels.

Study measures

Blood sampling

Blood sampling and other data acquisition are performed immediately before study drug administration (time point 0) and at 2, 3, 4, 8, 12-18, and 18-24 hours, or the last time point a participant is available. Reasons for non-availability include discharge from ED or hospital, loss of IV access, and participant sleeping. Blood samples are obtained at each time point for plasma MK assays. Blood for plasma LTE_4 assays and hepatic panels are drawn at time point 0 and the last time point the participant is available. All samples are immediately placed on ice, transported to the Clinical Research Center for storage, and frozen at -80° C.

Outcome measures

Objective and hypothesis 1 outcome, plasma MK C_{max}

Montelukast plasma assays are conducted in the Pharmaceutical Sciences Research Center at Lipscomb University under Good Clinical Practice guidelines. A six-point standard curve for montelukast ranging from 10-25000 ng/ml with four levels of quality control samples (30, 300, 3000,15000 ng/ml) is prepared using blank human plasma (BioIVT, Westbury, NY). Standards are prepared fresh from methanol stock solutions prior to each analytical run. All samples are protected from light and thawed on ice. An aliquot of 20 microliters of plasma for each standard, quality control sample, and subject sample is transferred to a 96-well plate containing 250 microliters of ice-cold acetonitrile spiked with montelukast-d6 (internal standard; 100 ng/ml). Samples are mixed thoroughly and centrifuged for 5 min at 3000 rcf. The supernatant is transferred to a new 96-well plate and dried under a gentle stream of nitrogen gas at 40°C. Sample residues are reconstituted with 400 microliters of mobile phase prior to analysis. Samples are loaded into a CTC Analytics PAL-xt DW Autosampler and 5 µL is injected into a Shimadzu LC-20 AD Series HPLC System coupled to a Sciex 6500 QTrap mass spectrometer (Foster City, CA). Analytes are separated on a C-18 column (50×2.1 mm, 1.7 µm, Phenomenex, Torrance, CA) heated to 60°C using a 70:30 (v/v) mobile phase mixture of 0.1% formic acid in water (mobile phase A) and 0.1% formic acid in acetonitrile (mobile phase B) at a flow rate of 0.5 mL/min. The gradient for mobile phase B is increased from 30 to 90% over 0.4 minutes, held at 90% for 1.1 minutes, and returned to 30% over 0.2 minutes with a total run time of 3 minutes. Detection of montelukast and montelukast-d6 is carried out by LC-

MS/MS analysis with electrospray ionization set in the positive ion mode followed by multiple-reaction monitoring of precursor and product ions for montelukast (m/z 586.2 to 422.2) and montelukast-d6 (m/z 592.2 to 428.2). The analytical method is validated with a within assay accuracy and precision of <10% and a between assay accuracy and precision of <15%.

Following quantitative bioanalysis, iIndividual MK concentrations for each time point are imported into Phoenix WinNonlin 8.0 software (Certara USA, Inc., Princeton, NJ) to generate a plasma concentration-time profile for each subject.

Noncompartmental analysis (Model 200: Plasma; Single Extravascular Dose; Linear Log Trapezoidal method) is performed on each individual plasma concentration-time profile to estimate the maximum observed plasma concentration (C_{max}), time to the maximum observed plasma concentration (T_{max}), the area under the concentration-time curve (AUC), the elimination rate constant (ke), elimination half-life, apparent oral volume of distribution (Vd/F), and apparent oral clearance (Cl/F) for each dose level of MK.

MK doses (mg/kg) for dose levels 2 and 3 are determined by PK-guided modeling using C_{max} data from preceding dose levels. This approach is consistent with FDA "Good Review Practice." PK analysis is performed after every 10 participants per dose level to determine if C_{max} has met the futility criterion for continuing or advancing to the next dose level.

At each dose level, a PK report is generated and updated after each Group to include individual participants' PK parameters and the cumulative number of participants that have failed to achieve the target C_{max} of 1700 ng/ml relative to the total number of participants enrolled at that Dose Level (Primary Endpoint). PK data is also used by the investigative team on an ongoing basis to model and simulate drug exposure to further identify and refine dose recommendations for subsequent Dose Levels.

At the completion of the dose escalation study, dose-dependent PK exposure parameters (C_{max} and AUC) will be evaluated to assess linearity of MK drug exposure across dose levels. Although C_{max} is the primary PK endpoint for dose determination that will be used in a future clinical trial to definitively evaluate the efficacy of high dose oral MK, additional samples collected during the elimination phase will provide a more robust PK assessment to complement safety assessments. MK concentrations from all participants will be combined to estimate population PK parameter estimates in children using Phoenix NLME 8.0 software (Certara USA, Inc., Princeton, NJ). During the population PK model building process, successful parameter minimization, diagnostic plots, plausibility and precision of each parameter estimate, as well as objective function and shrinkage values will be used to assess model appropriateness. Parameter precision for the final population PK model will be evaluated using nonparametric bootstrapping.

Objective/hypothesis 2 outcome

Hypothesis 2 evaluates clinical efficacy in a parallel-group randomized comparison. We hypothesize that MK produces a ≥2-point greater improvement in AAIRS at 4 hours versus placebo. The primary analysis is ANCOVA for AAIRS change, adjusted for baseline AAIRS (intention-to-treat). The AAIRS is a validated bedside asthma severity score comprising 7 components that reflect relevant exacerbation domains.[26] It is scored 0-16 points (16 most severe), with scores 7-11 categorized as moderate and 12-16 severe, and is measured at the blood sampling time points above. It has been validated against %-predicted FEV_1 and airway resistance by impulse oscillometry and as a predictor of the need for hospital or intensive care admission.[26]

Objective/hypothesis 3 outcome

Hypothesis 3 estimates the exposure-response relationship among MK recipients. Because this analysis is observational and subject to confounding, we will model AAIRS change at 4 hours as a function of C_{max} adjusting for baseline AAIRS, viral PCR, and plasma LTE_4.

Other measurements

We perform PCR testing of a nasal swab for respiratory viral detection to examine associations with outcomes and statistical interactions with plasma LTE_4 levels.

Asthma medication administration

We record all treatment administered during each time interval (e.g., 0-2 hr, 2-4 hr, 4-6 hr). These include systemic CCS, albuterol (MDI, one-time/continuous nebulization), magnesium, terbutaline, epinephrine, aminophylline, heliox, bilevel positive airway pressure (BiPAP), high-flow nasal cannula (HFNC), and/or endotracheal intubation and mechanical ventilation. For participants admitted to hospital, site of admission (PICU or floor) is recorded.

Statistical design and power

Hypothesis 1

We are primarily interested in estimating the change in plasma concentrations of MK over time and will report summary statistics at each time point numerically and graphically. We will also summarize the longitudinal measurements by the C_{max}, the proportion of subjects achieving a C_{max} of at least 1,700 ng/ml, time (T_{max}) to reach C_{max}, and time to reach 1,700 ng/ml (T_{1700}). While we anticipate being able to monitor all subjects for 24 hours, our primary analysis will consider subjects who

have at least 4 hours of blood draws to allow minimally sufficient time to achieve C_{max}.

For operating characteristics and sample size selection, we considered the probability of successfully finding a dose at which at least 86% of participants achieve a C_{max}≥1,700 ng/ml. In collaboration with the FDA, the sample size was set at 45 for each RCT arm based on adequate and inadequate dose scenarios described below.

We first considered the adequate dose scenario in which at least 13 of the 15 (86.7%) group participants successfully achieves a C_{max}≥1,700 ng/ml. The probability of successly identifying this dose is adequate will depend on p, the true probability that a dose will lead to a C_{max} above 1,700 ng/ml. If p=0.90, there is 82% power that we will observe 13 or more successes in 15 subjects; if p=0.95, there is 96% power we will observe 13 or more successes. These calculations are based on a one-tailed cumulative binomial distribution function with n=15, but there is the possibility of carryover leading to a dose level n of 20, 25, or 30. For n=25 and p=0.90, there is a 76% power we will observe 22 or more successes; if p=0.95, there is 97% probability of observing 22 or more successes.

Second, we considered the scenario of an inadequate dose that needs to be escalated. In this scenario, we would escalate to the next dose when more than 2 subjects have a C_{max} below 1,700 ng/ml after enrolling 5, 10, or 15 subjects. If a given dose is only 50% effective (p=0.5) in achieving a C_{max} above 1,700 ng/ml, the probability of meeting escalation criteria is 50% after 5 participants, 94% after 10 participants, or 99.6% after 15 participants.

Hypotheses 2

For the parallel group randomized clinical trial comparison, the primary clinical outcome is the mean difference in AAIRS change from baseline to 4 hours between MK and placebo groups. The primary analysis is ANCOVA for change in AAIRS with treatment as the factor and baseline AAIRS score as the covariate (intent-to treat). Results will be presented as adjusted mean differences with corresponding 95% confidence intervals. Pre-specified alternative strategies including modeling AAIRS scores as an ordinal outcome using the proportional odds ordinal logistic regression model and using mixed effects models to evaluate change in AAIRS scores using all post-baseline AAIRS measurements. As there is potential for missingness to be related to the outcome (subjects improving the most will have missing AAIRS measures), we will assume that all subject who are discharged home have the lowest AAIRS score. Sensitivity analyses will be used to evaluate the robustness of the results to this assumption.

Assuming a clinically important difference of 2 points in AAIRS change at 4 hours, a common SD of 3-4 points, α=0.05 (two-sided), and n=45 per arm, the trial provides 65-88% power depending on variance assumptions. Accounting for baseline AAIRS in ANCOVA increases power (e.g., to 80% if baseline explains 25% of variance when σ=4).

Hypotheses 3

We will test Hypothesis 3 in a multivariable linear regression model using change of the AAIRS as the outcome with C_{max}, pre-treatment AAIRS, and baseline plasma LTE_4 concentration among other clinically relevant covariates. Regression splines will be included as needed to allow for non-linear associations between predictors and the outcome as needed. As with hypothesis 2, if we find that the assumptions of the linear model are not appropriate, we will use the proportional odds ordinal regression model with the same outcome and predictors.

Power and sample size considerations are based on the 45 MK recipients. For bivariate correlations, we will have 80% power to detect correlations of 0.40 or greater (R^2 of 0.16). For the multivariable model calculation, if we assume that exacerbation severity and LT stress explain 20% of the variability in AAIRS change, then we have 80% power to detect if C_{max} explains an additional 12% of the variability in AAIRS change (improvement in R^2 of 0.12). If exacerbation severity and LT stress only explain 10% of the variability in AAIRS change, then we have 80% power to detect if C_{max} explains an additional 14% of the variability in AAIRS change (improvement in R^2 of 0.14). Calculations are based on a two-sided significance level of 0.05.

DISCUSSION

Asthma is the most common chronic disease of childhood and a frequent cause of hospital admissions. Hospitalization is needed most often because some airway inflammatory pathways are incompletely responsive to inhaled albuterol and systemic corticosteroid.[2-5]

LT synthesis by airway mast cells and eosinophils is induced by viral respiratory infection and aeroallergens, the most common asthma triggers in children.[8,9,13,36] LT-mediated airway inflammation is not CCS responsive and causes bronchoconstriction that is not entirely β-agonist responsive.[6] Addressing this inflammatory pathway has potential to substantially improve the health of children with acute exacerbations.

We present methods for an adaptive, double-masked RCT of high-dose oral MK in children with exacerbations that are moderate or severe after initial treatment with inhaled albuterol. The trial comprises escalating mg/kg dose levels determined by PK-guided dose modeling, added to standard treatment versus standard treatment alone.

The trial is adequately powered to test the primary hypothesis that at least one of the escalating mg/kg MK

doses achieves C_{max}≥1,700 ng/ml in ≥86% of participants. However, testing the secondary hypotheses that MK recipients will have >2 point improvement of the AAIRS and that C_{max} correlates with change of the AAIRS may have limited power to detect variability in AAIRS measurement over the course of participants' treatment in the ED. This reflects the challenge of identifying outcome measures for trials of acute asthma treatment. Notwithstanding this limitation, a consensus of asthma experts identified the AAIRS as an optimal outcome measure for studies of children with acute asthma exacerbations.[37]

Among strengths of the study are inclusion of participants who do not respond sufficiently to inhaled albuterol and are thus likely to have clinically meaningful LT-mediated airway inflammation that may respond to MK. In addition, PK parameters are assessed using state-of-the-art liquid chromatography coupled with tandem mass spectrometry, measures that make possible accurate identification of C_{max} at escalating mg/kg doses.

This research will yield knowledge to inform the design of a multi-site randomized trial of oral MK, powered for important clinical outcomes. This knowledge includes data to establish a well-tolerated, weight-based dose as well as preliminary data examining whether this treatment quickly decreases exacerbation severity to decrease hospitalizations.

CONCLUSION

Cysteinyl LTs are a likely cause of insufficient corticosteroid and β-agonist responsiveness that necessitate hospitalization in children with acute asthma exacerbations. Oral MK has potential to decrease the significant morbidity of these exacerbations. This research will provide critical data for dosing and design decisions for a future randomized trial sufficiently powered to definitively determine efficacy for acute exacerbations in this population.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee (Clinical trials registration NCT05819541)

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