

Acute Intervention Management Strategies (AIMS)

Hypothesis

Compared with conventional therapy (which consists of inhaled bronchodilators followed by the sequential addition of systemic corticosteroids) for the management of acute wheezing episodes in young children with intermittent asthma and severe exacerbations, intervention with an inhaled corticosteroid (ICS) or leukotriene receptor antagonist (LTRA) at the onset of respiratory tract illness (RTI)-associated symptoms will increase the proportion of symptom-free days over the 5-9 month study period.

A symptom-free day is defined as a day during which the child is free from symptoms consistent with asthma, including (1) cough, (2) any wheeze, (3) trouble breathing, (4) asthma associated interference with daily activities or awakening from sleep, and (5) no use of any medication for asthma, either preventative or in response to symptoms.

Background

Wheezing illnesses are common during the first years of life, with 20% of all children having at least one wheezing illness by one year of age (1), nearly 33% by 3 years of age, and almost 50% by 6 years of age (2). The majority of these episodes are triggered by viral respiratory tract infections (3, 4). Standard therapy for such illnesses in young children generally includes a stepwise addition of medications, typically commencing with a bronchodilator. If lower respiratory tract symptoms become increasingly severe or respiratory distress develops, oral corticosteroids often are added. Clinical experience indicates that young children with viral-induced exacerbations of wheezing may develop chest symptoms late in the illness and often respond poorly to this stepwise approach with continued worsening even after addition of corticosteroids at the onset of wheeze (now often 2-3 days after onset of respiratory tract symptoms). Such factors likely contribute to the high rate of Emergency Room visits and hospitalization for young children with asthma (5, 6). Thus, the current approach to a young child with severe intermittent asthma is inadequate.

Study findings of Tal et al. (7) and Brunette et al. (8) suggest that early corticosteroid therapy, ideally started at home, should impact on the progression of asthma episodes and decrease the rate of hospitalization for asthma. Young children who experience frequent exacerbations of asthma may receive several short courses of systemic corticosteroids per year. Individual courses of oral corticosteroids may be associated with behavioral side effects. In addition, Dolan et al reported that 20% of children who received 4 or more short courses of oral corticosteroids in the past year had impaired response to insulin-induced hypoglycemia (9). The potential toxicity of repeated courses of oral corticosteroids is a significant clinical concern and likely influences the behaviors of pediatricians faced with young children who wheeze following RTI-associated symptoms. The use of topical ICS in the treatment of acute exacerbations is likely to be accompanied by a greater safety profile and parental acceptance.

Previous studies indicate that the use of budesonide (ICS) leads to lower symptom scores, less wheezing, and a reduce requirement for oral corticosteroids (10, 11, 12).

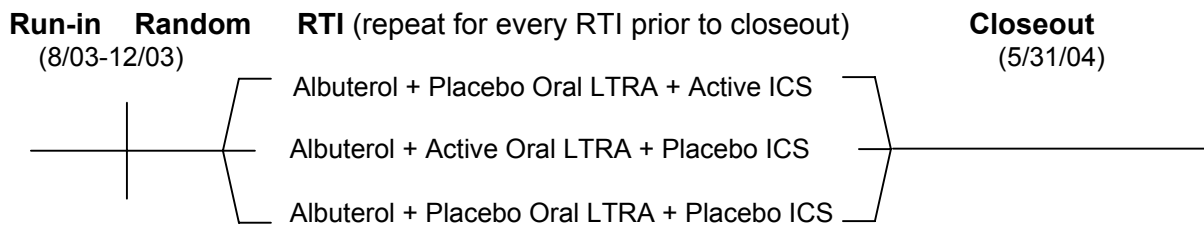
The cysteinyl leukotrienes (cysLTs) have been identified as important mediators in the complex pathophysiology of asthma. Findings suggest that, similar to asthma pathophysiology, cysLTs play a role in the pathophysiology of viral-induced wheeze and are not fully suppressed by the preferred standard anti-inflammatory therapy, ICS (13). Given the presence of cysteinyl leukotrienes (cLTs) in the airways of children with viral-induced wheezing, the addition of a drug that modifies the effects of leukotrienes might be expected to modify the clinical course of patients who wheeze with viral infections. Montelukast has recently has been shown to be safe and effective in children 2-5 years of age with persistent asthma (14). Patients who received montelukast 4mg daily for 12 weeks experienced significant reductions in asthma symptoms, albuterol use, and oral corticosteroid courses. Clinical improvements were present within 1 day of starting therapy. Given the presence and possible pathogenic role of cLTs in children with acute viral wheezing and the rapid onset of action of montelukast, the development of severe lower airway symptoms may be attenuated with the use of montelukast at the onset of symptoms in the context of a RTI.

Specific Aims

Specific Aims are to determine if the initiation of an ICS or LTRA with an inhaled β 2-agonist (albuterol) at the onset of RTI-associated symptoms:

1. Increases the proportion of symptom-free days over the entire treatment period during the trial.
2. Increases the time to initiation of the first course of oral corticosteroids for acute wheezing episodes.
3. Decreases the total number of courses and days of oral corticosteroids.
4. Decreases the duration and severity of lower respiratory tract symptoms, as reflected by the symptom scores in the 14-day periods following each initiation of study medication.
5. Decreases the total number of episodes of wheezing.
6. Prolongs the time to treatment failure, as defined as (1) 3 courses of oral corticosteroid, (2) 1 hospitalization for acute exacerbation of wheezing, (3) hypoxic seizure during an acute exacerbation of asthma/wheezing, or (4) intubation for acute asthma/wheezing.
7. Reduces measures of patient and family morbidity as reflected by days missed from daycare, parental work and caregiver quality of life.
8. Decreases the number of unscheduled visits for acute wheezing episodes (PCP office, urgent care, and ED/hospitalization).
9. Affects linear growth.
10. Improves markers of allergic inflammation (peripheral blood eosinophils and IgE) measured at the end of the treatment period compared to baseline.
11. Improves markers of airway inflammation (cyst-leukotrienes in nasal washings) during and immediately following acute episodes of RTI.
12. Determine if the patient genotype of polymorphisms in asthma-associated disease features or response to specific medications (such as beta2-adrenergic receptor and the 5-lipoxygenase gene) influences or predicts the response to the different therapeutic approaches.
13. Determine if the patient phenotype of factors associated with persistence of wheezing as reflected by the Asthma Predictive Index (1) influences or predicts the response to therapy.

Study Design



The selected design of this study is a randomized, double-blind, double-dummy placebo-controlled parallel comparison of three strategies directed at minimizing symptoms of wheezing during acute RTIs in children 12-59 months of age with histories of moderate-severe episodes of wheezing. There will be a 2-week observation period to qualify and characterize children. During this 2-week period, patients will have no lower respiratory tract symptoms other than mild cough (to assure the presence of intermittent disease) and parents will be able to use diary cards with $\geq 80\%$ completeness. Patients will then be randomized to one of three treatment groups and followed for the remainder of the fall-winter-early spring season, during which the participants will receive one of the following regimens for 7 days at the first-sign of RTI-associated symptoms:

- (1) Active ICS and placebo LTRA and albuterol inhalation treatments four times daily, or
- (2) Active LTRA and placebo ICS and albuterol inhalation treatments four times daily, or
- (3) Placebo ICS and placebo LTRA and albuterol inhalation treatments four times daily.

Additional rescue albuterol treatments may be administered on an as needed basis. These intervention treatments will be repeated with each subsequent illness characterized by RTI-associated symptoms. Oral corticosteroids will be available for all children at home and will be started based upon a specific algorithm.

We will enroll 225 children (45 children per clinical center) 12-59 months of age who meet all inclusion criteria and do not have any of the exclusion criteria. Children will be randomized to one of the three treatment arms (90 on each active therapy and 45 on conventional therapy).

Timeline

Recruiting for the AIMS study will begin June 2003. The study will run from Aug 2003 until a common closeout period during the last two-weeks of May 2004.

Summary

Wheezing illnesses are common during the first several years of life and pose a significant clinical problem to the practicing physician. These illnesses are associated with significant morbidity ranging from symptoms of cough, wheeze, dyspnea, sleep disturbance, time lost from school and parental work, and hospital care for urgent visits and hospitalizations. While prior investigations have attempted to identify practical and effective interventions aimed at halting the progression of these illnesses, the results have been disappointing. An effective approach to this problem would provide a sizeable benefit to these children.

Through this trial, we will evaluate the effect of 3 intervention strategies in children age 12 months - 59 months with recurrent wheezing in the context of RTIs of sufficient severity to have resulted in previous treatment in the emergency unit, hospitalization, or urgent visit to a physician's office. We will attempt to answer the following questions:

1. Does early treatment with ICS or LTRA change the course of severe intermittent asthma over the study period compared with conventional therapy?
2. Can the response to either intervention be related to either phenotypic (eosinophils, IgE, cysLT in nasal lavage, asthma predictive index positive/negative) or genotypic (such as β 2-adrenergic receptor or 5-lipoxygenase gene) features?

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