IRB Protocol
Sarah Taylor-Black
8/5/08

Randomized Comparison of Strategies for Reducing Treatment in Moderate Persistent Asthma

A. Study Purpose and Rationale

Treatment guidelines for asthma recommend the use of inhaled corticosteroids and long-acting inhaled beta 2-agonists as first-line therapy in patients with moderate persistent asthma or a higher dose of inhaled corticosteroid.[1,2,3] When asthma control has been achieved, the guidelines further recommend the "stepping down" of therapy to minimize the adverse effects of medication.

It has not yet been systematically investigated whether, in patients with moderate persistent asthma that is well-controlled with the use of a low-dose inhaled corticosteroid (ICS) and long-acting inhaled beta2-agonist (LABA) twice daily, therapy can be stepped down to an alternative treatment strategy, eliminating the LABA with the addition of a leukotriene receptor antagonist (LTRA) without the loss of asthma control.[4,5] Studies have shown that patients achieving asthma control with fluticasone propionate/salmeterol 250/50 mcg twice daily, stepping treatment down to a lower dose of fluticasone propionate/salmeterol 100/50 mcg twice daily was more effective than switching to an inhaled corticosteroid alone.[6] However, eliminating the LABA from the treatment regimens may be important given recent review articles suggesting increased adverse events with the use of these medications. The Cochrane Database of Systematic Review has shown that serious adverse events were increased in clinical trials comparing regular salmeterol to placebo. Although the increase in asthma-related mortality was smaller and insignificant in patients taking inhaled corticosteroids with salmeterol, the confidence interval is wide, so it could not be concluded that the ICS abolish the risks of regular salmeterol (OR 1.52, CI 0.51-4.49).[7] In addition, a meta-analysis published in the Annals of Internal Medicine looking specifically at the effects on serious asthma-related events of adding salmeterol to ICS concluded that although salmeterol combined with ICS decreased the risk for severe exacerbations, it and may or may not alter the risk for asthma-related deaths or intubations compared with ICS alone.[8]

Therefore, removing a LABA from a treatment regimen to add a LTRA may be safer for patients. Montelukast as add-on therapy to ICS has been shown to improve control of mild to moderate asthma compared with ICS monotherapy. Although the addition of salmeterol to ICS is clinically as effective as or even more effective than the addition of montelukast, montelukast may have a better long term safety profile and offer a treatment alternative for asthma patients.[9,10]

B. Study Design and Statistical Procedures

In patients with asthma that is well-controlled with twice-daily use of inhaled corticosteroid and long-acting beta 2 agonist (fluticasone 100mcg and salmeterol 50mcg), I will investigate the following step-down treatment strategies: fluticasone 100mcg twice daily plus montelukast 10mg once daily (the primary alternative) or fluticasone 100mcg twice daily (the secondary alternative).

Outcome variables

The primary outcome measure will be the time to treatment failure, defined as the occurrence of any of the following events: hospitalization or an urgent medical visit for asthma initiated by the patient or physician; use of systemic corticosteroids for asthma or the need for increased dose of inhaled corticosteroids for asthma as determined by the study physician or an asthma care provider; a decrease in prebronchodilator FEV1 to more than 20% below the baseline value measured at randomization; a decrease in morning peak expiratory flow rate to more than 35% below the baseline value on 2 consecutive days; use of 10 puffs or more per day of rescue beta-agonist for 2 consecutive days (except as a medication before exercise); refusal of the patient to continue because of lack of satisfaction with treatment; or judgement by a physician that the patient should stop treatment for reasons of safety. Follow-up would continue according to protocol after the treatment failures were noted.

Secondary outcomes specified in the protocol included measures of pulmonary function (morning peak expiratory flow rate from the patients' daily diary cards and FEV1), measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores on the Asthma Control Questionnaire.[11]

Study Design

Double-blind, randomized, placebo-controlled trial.

Participants will be randomized to received one of the 3 study treatments with an allocation ration (1:1:1). The randomization schedule will be a permuted block design stratified by clinic. The double-masked treatment period will last 16 weeks, and patients will visit the clinic after the 2, 4, 8, 12, and 16th week of blinded treatment.

Statistical Analysis

Analyses will be performed by intention-to-treat. Kaplan-Meier[12] and Cox proportional-hazards regression techniques[13] will be used to evaluate time-to-treatment failure. Linear and logistic-regression models will be used to evaluate differences among treatment groups for continuous and dichotomous outcomes, respectively.

Sample Size:

The numbers will be chosen for the study to have a statistical power of 80% to detect an absolute difference of 10% or more in the percentage of patients with a treatment failure between the fluticasone plus montelukast group or fluticasone group and

the fluticasone-salmeterol group.[14] This yields a treatment group size of approximately 313, meaning that the study in total would include approximately 939 participants.

C. Study Procedures

Diskus counters will be checked at each visit to determine adherence to the treatment regimen. Participants and staff will be masked to the study treatment. At randomization, each participant will be instructed to use the discus inhalers twice each day. Each participant will also take a capsule containing montelukast or placebo each day in the evening. Treatment compliance will be determined two ways, from diary card and by checking counters on inhalers and pill counts.

D. Study Drugs or Devices

Study drugs will include a combination therapy with fluticasone propionate inhalation powder 100 mcg and salmeterol 50 mcg bid, fluticasone propionate inhalation powder 100mcg bid with montelukast 10mg qpm, and fluticasone propionate inhalation powder 100mcg bid. Placebo and matching montelukast tablets will be prepared.

E. Study Questionnaires: None

F. Study Subjects

Inclusion Criteria: Inclusion criteria for the run-in period, during which open-label fluticasone 100mcg and salmeterol 50mcg was given twice daily for 4 to 6 weeks, included physician-diagnosed asthma; an age of 15 years or older and a forced expiratory volume in 1 second (FEV1) of 60% or more of the predicted value before administration of a bronchodilator; and a reversibility of airway obstruction by 12% or more with the use of a beta-agonist or a provocative concentration of methacholine producing a 20% decrease in FEV1 of 8mg per milliliter or less within the previous 2 years.

Inclusion criteria for randomization after the run-in period were as follows: adequate adherence (i.e., completion of at least 10 of the previous 14 days of daily diary cards and fluticasone treatment for at least 21 of the previous 28 days); a prebronchodilator FEV1 of at least 80% of the predicted value; fewer than 16 puffs of a rescue beta-agonist used per week during the final 2 weeks of the run-in period (except as medication before exercise); no hospitalization, urgent medical care (for asthma), oral corticosteroid use, or use of additional asthma medication during the run-in period; and an absence of febrile illness (temperature exceeding 38.0°C, or 100.4°F) within the previous 24 hours.

G. Recruitment of Subjects

All subjects will provide written, informed consent. Patients will be recruited from Asthma Clinical Research Center Clinics and assessed for eligibility.

H. Confidentiality of Study Data

Subject confidentiality will be maintained throughout the study by using a unique code to identify each subject. The code will only be accessible to investigators of the study. All data collected will be stored in a safe area that is accessible to the study investigators alone.

I. Potential Conflict of Interest: None

J. Location of the Study

Subjects for this study will be enrolled from the patient population at New York Presbyterian Hospital-Columbia University Medical Center out-patient Asthma and Pulmonary clinics as well as from additional Asthma Clinics affiliated with other medical research centers participating in the study.

K. Potential Risks

The potential risks to the subjects of the trial include side effects from the drugs used in the study. As we are studying step-down treatment, there is also a risk of worsening asthma symptoms potentially leading to hospitalization, intubation, days missed from work, etc.

L. Potential Benefits

The potential benefits of this study include reduced toxicity from LABA in patients of the treatment arms not taking this medication. They also include free medications for several weeks.

M. Alternative Therapies: None

N. Compensation to Subjects: None

O. Costs to Subjects: None

P. References

[1] Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda, MD: National Institutes of Health, 1995.
[2] National Asthma Education and Prevention Program. Executive Summary of the NAEPP expert panel report: guidelines for the diagnosis and management of asthma – Update on selected topics 2002. Bethesda, MD: National Institutes of Health, 2002.
[3] National Asthma Education and Prevention Program. Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. Bethesda, MD: National Institutes of Health, 2007.

[4] Foresi A, Mastropasqua B, Chetta A, D'Ippolito R, Testi R, Olivieri D, Pelucchi A. Step-down compared to fixed-dose treatment with inhaled fluticasone propionate in asthma. Chest. 2005 Jan;127(1):117-24.
[5] Bacharier LB. "Step-down" therapy for asthma: why, when, and how? J Allergy Clin Immunol. 2002 Jun;109(6):916-9.
[6] Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006 Mar;117(3):563-70. Epub 2006 Jan 27.
[7] Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD006363.
[8] Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, Yancey S. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med. 2008 Jul 1;149(1):33-42.
[9] Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T, Schneider A. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. Thorax. 2008 May;63(5):453-62.
[10] Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, D'Orazio N. Antileukotriene drugs: clinical application, effectiveness and safety. Curr Med Chem. 2007;14(18):1966-77.
[11] Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-907
[12] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-481.
[13] Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
[14] American Lung Association Asthma Clinical Research Centers, Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, Wise RA. Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med. 2007 May 17;356(20):2027-39.