

Characterizing the Response to a Leukotriene Receptor Antagonist (LTRA) and an Inhaled Corticosteroid (CLIC)

Research Hypothesis

The proposed research hypothesis for the CLIC trial is as follows:

In children with mild to moderate persistent asthma, there may be considerable difference within individual subjects in the magnitude of response as determined by improvement in FEV₁, for inhaled fluticasone propionate and montelukast when they are administered at recommended doses. This variation in response may be related to the patient's asthma phenotype and/or genotype associated with asthma, allergy or the pathways for metabolism or receptors associated with medications used to treat asthma.

Despite the variety of long-term control medications available for asthma therapy, there remains confusion and continued controversy as to the response to these agents for individual patients. Because of this, the choice of a long-term control medication is often made based on convenience, such as ease of administration, and relative safety. The confusion surrounding the choice of a long-term control medication is confounded by the introduction of new classes of medications, alternatives within a class of medications, and novel drug delivery systems. The goal of this trial is to determine the feasibility of identifying a method to associate response to a medication through changes in pulmonary function with the phenotypic features of asthma and the genotype of the individual. Ultimately, we would like to determine whether the identification of an asthma phenotype and the individual's genotype can be used to predict the response to a medication.

In this initial study, we will evaluate children ages 6 to 18 years of age with mild to moderate persistent asthma (FEV₁ ≥ 70% predicted) and a bronchodilator response (≥ 12% improvement of FEV₁ after treatment with albuterol metered dose inhaler) to answer the following questions:

Is response to inhaled fluticasone propionate independent of the response to oral montelukast when they are administered over separate treatment periods?

Are there subgroups of patients that respond favorably to both medications?

Can the response to each medication be related to an asthma phenotype and/or the individual's genotype?

It is clear from previous work that inhaled glucocorticoids are the preferred medication for the management of moderate to severe persistent asthma. However, concerns regarding the risk for adverse effects have resulted in hesitancy to utilize inhaled glucocorticoids as the first line medication in the management of mild persistent asthma. The orally administered leukotriene receptor antagonists are easily administered and appear safer than inhaled glucocorticoids. Physicians have questioned whether methods could be derived to assist in the selection of medications as first-line long-term control therapy.

Background and Rationale

Asthma is a chronic respiratory disease characterized by reversible airflow limitation and airway hyperresponsiveness to a variety of stimuli (1). Mucosal inflammation within the airways has been associated with severe, fatal asthma (2), and recent studies using the flexible fiberoptic bronchoscope have also documented mucosal inflammation within the airways of moderate and even mild asthmatics (2-5). The preponderance of information suggests that airway inflammation is responsible for many of the clinical manifestations of asthma.

Refractoriness to oral glucocorticoid (GC) therapy has been demonstrated in patients with severe persistent asthma, for example, less than 15% improvement in FEV₁ following a course of oral glucocorticoid therapy in patients with FEV₁ less than 70% predicted (6-8). It is not clear whether refractoriness to glucocorticoid therapy occurs in patients with mild and moderate persistent asthma treated with inhaled glucocorticoids. Defining this population has not been attempted to date. Similarly, variation in pulmonary response to leukotriene modifiers has not been evaluated. Response to therapy in older children and adults is presently measured by clinical parameters and pulmonary function parameters, specifically FEV₁. It would be useful to define easy and reliable methods to characterize response to inhaled glucocorticoid and leukotriene antagonist therapy. This information could then be used to identify potential mechanisms for variation in response, for example, features of drug metabolism, receptor expression, or mediator synthesis. If a level of response with these medications can be related to an asthma phenotype and/or genetic polymorphisms, it is possible that this information could be used in a prospective manner to select medications that would most likely result in a favorable clinical response.

Potential explanations for variation in response to glucocorticoid therapy in severe asthma patients has been related to altered drug disposition, glucocorticoid receptor abnormalities, glucocorticoid receptor β expression, increased transcription factors, and increased expression of pro-inflammatory cytokines (7-21). Pharmacokinetic abnormalities are often associated with induction of steroid metabolism related to anticonvulsant therapy but there are also significant

variations in elimination in the absence of enzyme inducers and inhibitors (9). Mechanisms for this intrinsic variation in metabolism have not been explored and related to the variation in response to steroid therapy in asthma patients (10).

A recent report by Malmstrom et al demonstrates the significant variation in response to inhaled beclomethasone dipropionate and montelukast in adult patients with chronic asthma (22). This parallel study of beclomethasone dipropionate and montelukast in adults sponsored by Merck, Inc. indicated that the response to therapy can vary considerably for both medications. On average, the response to oral montelukast was approximately 70% of that obtained with inhaled beclomethasone dipropionate. Based on standard comparison studies such as this report, it is often assumed that patients respond to both medications with a comparatively better response to inhaled steroids. However, it is interesting to examine the variability of response within the two treatment groups. Patients varied from having no response to those having greater than 30% increase in FEV₁ to each treatment, with an average increase of 10%. Approximately 25% of the patients failed to improve FEV₁ following inhaled beclomethasone dipropionate and approximately 33% failed to increase FEV₁ following montelukast therapy. To date, a crossover study has not been performed to determine whether the response to one medication is completely independent of the response to the alternative medication.

In clinical management, perhaps these two treatments could be used more effectively if patients were characterized based on asthma phenotype or genotype prior to initiating treatment. This information could be then used to select the most appropriate treatment or to modify the therapeutic regimen, for example, administering a higher daily dose of the medication or administering the medication in shorter dosing intervals.

The CLIC protocol will examine the variation in response to an inhaled glucocorticoid and a leukotriene receptor antagonist in children with mild to moderate persistent asthma characterized for asthma phenotype. The response to the two medications will be evaluated in individual patients. This data base will be used to identify phenotypes of response and to relate this response to the patient's asthma phenotype and to selected genetic markers, related to disease, drug receptors, and drug metabolism.

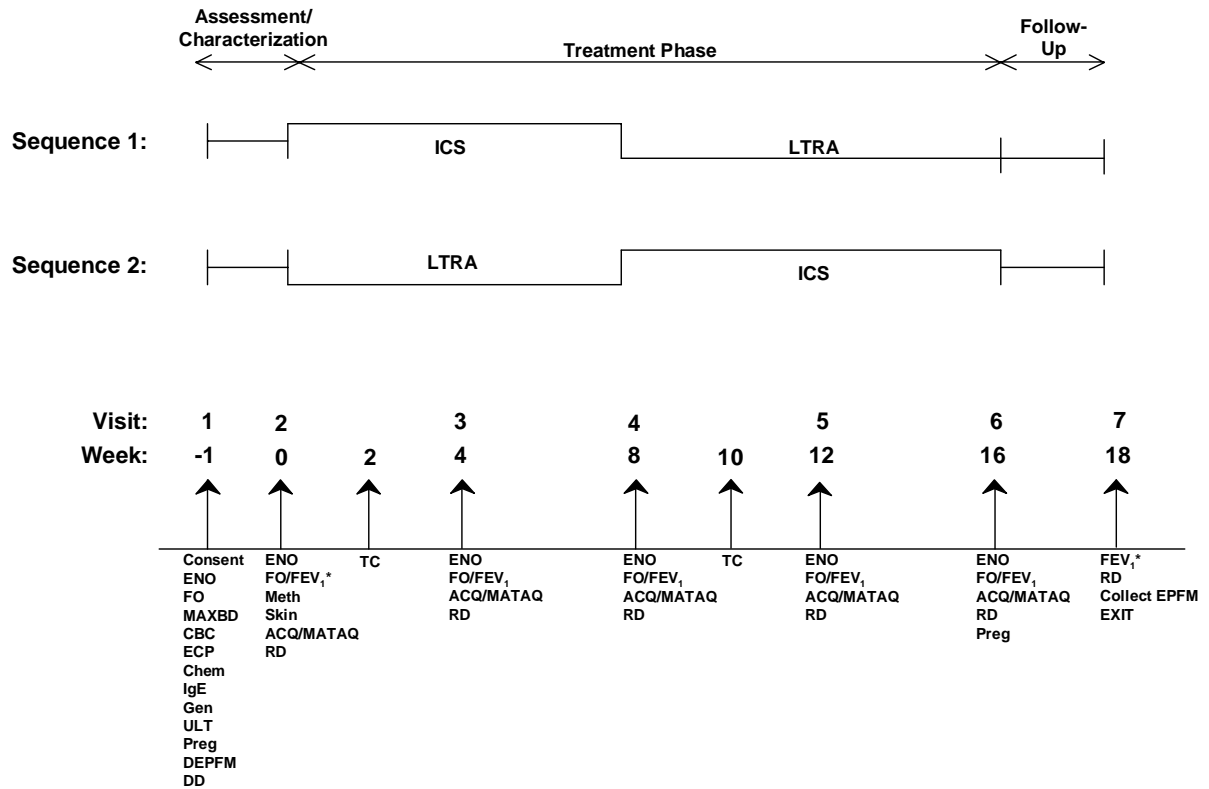
Specific Aims

1. To determine if response to inhaled fluticasone propionate is independent of the response to montelukast in children with mild to moderate persistent asthma.

2. To isolate patient populations that respond favorably to both medications, to one medication but not the other, and poorly to both medications.
3. To examine whether the patient's asthma phenotype and genotype for selected markers can be linked to the response to inhaled fluticasone propionate and montelukast in this carefully characterized patient population.

Study Design

The selected design of this study is a randomized, double-blind crossover study, comparing montelukast to inhaled fluticasone propionate in mild-to-moderate persistent asthma in 210 children of ages 6 to 18 years. There will be a one-week assessment/characterization period to qualify and characterize patients. Children will be randomized to one of two crossover treatment sequences and receive active leukotriene receptor antagonist (LTRA) for 4 weeks and fluticasone propionate (ICS) for 8 weeks.



ACQ = Asthma Control Questionnaire; MATAQ = Modified Asthma Therapy Assessment Questionnaire; CBC = complete blood count, total eosinophil count; Consent = Obtain Informed Consent; ECP = plasma eosinophilic cationic protein; Chem = chemistry; IgE = serum IgE; Preg = pregnancy test in those reaching menarche; ENO = exhaled nitric oxide; DD = dispense diary; DEPFM = dispense electronic peak flow meter; RD = review symptom diary; FO/FEV₁ = forced oscillation and spirometry before and after bronchodilator treatment (* indicates no bronchodilator testing at this visit); ULT = urinary leukotriene measurement; max BD = maximal bronchodilator response; Gen = genetics analysis; Skin tests = allergen skin tests; TC = Telephone Call; EXIT = completion and discharge from study. Treatments: ICS = inhaled corticosteroid. Inhaled fluticasone propionate (Flovent Diskus® 100 mcg per inhalation) or corresponding placebo administered as one inhalation twice daily. LTRA = leukotriene receptor antagonist. Montelukast tablet (5 mg for those 6 to 14 years and 10 mg for those 15 to 18 years) or corresponding placebo administered as one tablet once daily at night.

This is a two-sequence crossover study incorporating a leukotriene receptor antagonist (LTRA) and an inhaled corticosteroid (ICS) and their corresponding placebo formulations. The treatments selected are based on the availability of published dosing schedules specific for the age group and level of severity to be included in this study protocol. The LTRA is montelukast oral tablet (5 mg for those 6 to 14 years and 10 mg tablet for those 15 to 18 years of age) administered as one tablet by mouth at night. The ICS is fluticasone propionate (100 mcg per inhalation, Diskus®) administered as one inhalation twice daily. A mouth-rinsing technique will be applied following the inhaled fluticasone propionate administration to minimize oral absorption. During an active LTRA treatment period, the subject will receive active LTRA and placebo ICS. During an active ICS treatment period, the subject will receive active ICS and placebo LTRA. At

each visit, the subject will be given a set of new medications. A supply will be given sufficient for the time to the next visit to allow for small variations in the visit time.

Timelines

The CLIC trial will initiate enrollment of patients in January 2002. It is anticipated that the last patient visits will occur in February 2003.

References

1. National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health, National Heart, Lung, and Blood Institute, Publ. No. 97-4051, 1997.
2. Dunhill MS. The pathology of asthma with special reference to changes in the bronchial mucosa. *J Clin Pathol* 1960;13:27-33.
3. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Respir Dis* 1985;131:599-606.
4. Robinson DS, Hamid Q, Ying S, Tsicopoulos A, Barkans J, Bentley AM, Corrigan C, Durham SR, Kay AB. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326:298-304.
5. Bousquet J, Chanez P, Lacoste JY, Barneon G, Ghavanian N, Enander I, Venge P, Ahlstedt S, Simony-Lafontaine J, Godard P, Michel F-B. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;323:1033-9.
6. Schwartz HJ, Lowell FC, Melby JC. Steroid resistance in bronchial asthma. *Ann Intern Med* 1968;69:493-9.
7. Lee TH, Brattsand R, Leung DYMe. Corticosteroid action and resistance in asthma. *Am J Respir Cell Mol Biol (Suppl)* 1996;93:S1-S79.
8. Sher ER, Leung DYM, Surs W, Kam JC, Zieg G, Kamada AK, Szeffler SJ. Steroid-resistant asthma. Cellular mechanisms contributing to inadequate response to glucocorticoid therapy. *J Clin Invest* 1994;93:33-9.
9. Hill MR, Szeffler SJ, Ball BD, Bartoszek M, Brenner AM. Monitoring glucocorticoid therapy: a pharmacokinetic approach. *Clin Pharmacol Ther* 1990;48:390-8.
10. Kamada AK, Spahn JD, Surs W, Brown E, Leung DYM, Szeffler SJ. Coexistence of glucocorticoid receptor and pharmacokinetic abnormalities: factors that contribute to a poor response to treatment with glucocorticoids in children with asthma. *J Pediatr* 1994;124:984-6.

11. Chrousos GP, Vingerhoeds A, Brandon D, Eil C, Pugeat M, DeVroede M, Loriaux DL, Lipsett MB. Primary cortisol resistance in man. A glucocorticoid receptor-mediated disease. *J Clin Invest* 1982;69:1261-9.
12. Hurley DM, Accili D, Stratakis CA, Karl M, Vamvakopoulos N, Rorer E, Constantine K, Taylor SI, Chrousos GP. Point mutation causing a single amino acid substitution in the hormone binding domain of the glucocorticoid receptor in familial glucocorticoid resistance. *J Clin Invest* 1991;87:680-6.
13. Leung DYM, Hamid Q, Vottero A, Szeffler SJ, Surs W, Minshall E, Chrousos GP, Klemm DJ. Association of glucocorticoid insensitivity with increased expression of glucocorticoid receptor beta. *J Exp Med* 1997;186:1567-74.
14. Poznansky MC, Gordon AC, Douglas JG, Krajewski AS, Wyllie AH, Grant IW. Resistance to methylprednisolone in cultures of blood mononuclear cells from glucocorticoid-resistant asthmatic patients. *Clin Sci* 1984;67:639-45.
15. Corrigan CJ, Brown PH, Barnes NC, Tsai JJ, Frew AJ, Kay AB. Glucocorticoid resistance in chronic asthma. Peripheral blood T lymphocyte activation and comparison of the T lymphocyte inhibitory effects of glucocorticoids and cyclosporin A. *Am Rev Respir Dis* 1991;144:1026-32.
16. Alvarez J, Surs W, Leung DYM, Iklé D, Gelfand EW, Szeffler SJ. Steroid-resistant asthma: immunologic and pharmacologic features. *J Allergy Clin Immunol* 1992;89:714-21.
17. Adcock IM, Lane SJ, Brown CR, Peters MJ, Lee TH, Barnes PJ. Differences in binding of glucocorticoid receptor to DNA in steroid-resistant asthma. *J Immunol* 1995;154:3500-5.
18. Spahn JD, Leung DYM, Surs W, Harbeck RJ, Nimmagadda S, Szeffler SJ. Reduced glucocorticoid binding affinity in asthma is related to ongoing allergic inflammation. *Am J Respir Crit Care Med* 1995;151:1709-14.
19. Kam JC, Szeffler SJ, Surs W, Sher ER, Leung DYM. Combination IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. *J Immunol* 1993;151:3460-6.
20. Spahn JD, Szeffler SJ, Surs W, Doherty DE, Nimmagadda SR, Leung DYM. A novel action of IL-13: induction of diminished monocyte glucocorticoid receptor-binding affinity. *J Immunol* 1996;157:2654-9.
21. Leung DYM, Martin RJ, Szeffler SJ, Sher ER, Ying S, Kay AB, Hamid Q. Dysregulation of interleukin 4, interleukin 5, and interferon gamma gene expression in steroid-resistant asthma. *J Exp Med* 1995;181:33-40.
22. Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Wei LX, Seidenberg BC, Reiss TF. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med* 1999;130:487-95.