Treatment of Chronic Stable Asthma with Drugs Active on the 5-Lipoxygenase Pathway

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Key Words

Zileuton
Leukotriene
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Abstract

It is now established that 5-lipoxygenase products are synthesized and released in the airway during asthmatic reactions. The importance of these products in the asthmatic response has been established through study of the effects of 5-lipoxygenase inhibitors and leukotriene D₄ receptor antagonists in patients with chronic stable asthma. In this study we review the data demonstrating that chronic administration of zileuton, an inhibitor of 5-lipoxygenase, is associated with improved airway function, decreased asthma symptoms and decreased need for asthma medication use in patients with mild to moderate asthma.

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Introduction

It is now known that agents capable of inhibiting the generation or action of 5-lipoxygenase products have a beneficial effect in asthma induced by, e.g., exercise, allergens or aspirin. Although the utility of agents active on the 5-lipoxygenase pathway has been established in these settings, an important question is their safety and efficacy in the long-term treatment of asthma.

Zileuton

The efficacy of zileuton as a treatment for chronic stable asthma was evaluated in 139 patients in a month-long double-blind, multi center, placebo-controlled trial [1]. Treatments with 600 mg zileuton four times a day, with 800 mg zileuton twice a day or with placebo were compared. The trial design consisted of a 1-week single-blind 'lead in' dummy treatment period followed by a 4-week double-blind treatment period. All patients took identical-appearing capsules four times per day which contained either zileuton (active drug alternating with placebo in the 800-mg treatment), or placebo.

Patients with asthma, an FEV₁ between 40 and 75% of predicted, a 15% bronchodilator response to 2 puffs of inhaled albuterol who required only inhaled β -agonists for control of their asthma were identified. During the single-blind placebo lead in and the double-blind study period, all patients took capsules four times a day. Each patient recorded peak expiratory flow rates in the morning and evening in a study diary. Rescue inhaler use and asthma symptoms were recorded in the same diary. During the 4-week double-blind period, patients returned to the study center at the same time of day on a weekly basis to have spirometry performed and to review diary cards

and medication use. Urine was collected for analysis of leukotriene E4 excretion during the lead in and on the last day of treatment.

139 patients completed the trial. The mean FEV₁ in the various treatment groups was between 55 and 61% of predicted. Morning peak flow rates were approximately 380-400 L/min in all treatment groups.

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On the first day of zileuton treatment, a maximum increase in FEV₁ of 14.6% was recorded 60 min after drug administration in the group receiving 600 mg of zileuton. This increase was significantly greater than that observed in the placebo group ($p < 0.001$). After 4 weeks of treatment, the group receiving zileuton, 600 mg 4 times a day, had a 13.4% improvement in the FEV₁ which was significantly greater than the FEV₁ change noted in the placebo treatment group ($p < 0.02$). There were also significant improvements in the group receiving zileuton, 600 mg 4 times a day, when compared to placebo, in morning peak flow, β -agonist use and asthma symptoms.

These data demonstrate that treatment with zileuton, a drug that blocks the action of the enzyme 5-lipoxygenase, is associated with improvements in both objective and subjective measures of disease severity in patients with mild to moderate asthma.

A New Asthma Treatment Paradigm

Currently, asthma treatment has been considered as either bronchodilator or 'anti-inflamator' [2, 3]. The development of agents active on the 5-lipoxygenase pathway provides a new category to treatment: mechanism-based therapy. In such therapy, treatment is based on the perceived pathobiology of asthma and success of a treatment establishes information about the asthma mechanisms.

References

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