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Clinical trial with ketotifen

To the Editor:

Recently, a letter to the editor, written by Dr. Kerrebijn,¹ commenting on the results of the multicenter clinical trial of ketotifen (Zaditen) in pediatric asthma by Rackham et al.² was published. In this reply, we would like to address the concerns raised by Dr. Kerrebijn regarding the description of the study design.

The study² was designed to evaluate the efficacy of ketotifen, a nonbronchodilator antiasthma drug, in the treatment of pediatric asthma. Treatment effectiveness was evaluated with the following parameters: (1) reduction of concomitant asthma medications (theophylline and β -agonist), (2) improvement in daily peak flow measurements, and (3) improvement in lung function (FEV₁, FVC, and FEF₂₅₋₇₅) measured by periodic spirometry. Criteria for reduction of dosage of concomitant bronchodilators are listed in the "Study outline" section of the article. Lung function and peak flow measurements were performed according to standard procedures. After a 4-week baseline period, 138 children with chronic asthma were randomly assigned to the study medication (69 assigned to ketotifen and 69 to placebo) by the central coordinator. Active drug and the placebo were identical in taste and color for both forms (syrup and tablets); differentiation by the physician was impossible. Eight to 19 evaluable patients in each of the 12 centers were entered in the efficacy analysis. Statistical tests for interaction group-by-investigator were performed and justified pooling of the data from all centers. The severity of asthma reported in Table I of the article² (ketotifen group: 37% mild, 63% moderate to severe; placebo group: 36% mild, 64% moderate to severe) was based on the physicians' evaluation of the interference of asthma symptoms with daily activities and sleep. Based on objective parameters, mean values of lung function, and peak expiratory flow rate (Table I), and on the fact that patients were not taking cromoglycate nor corticosteroids at entry, patients who were entered into the study had asthma of mild severity.

Notwithstanding the mildness of their asthma, all patients entering this clinical trial required asthma medication on a daily basis. The number of patients requiring long-term use of theophylline and the average daily dose of theophylline required to control their asthma symptoms were statistically lower ($p < 0.05$) in the ketotifen-treated group than in the placebo-treated group. This observation was made from week 14 until the end of the study (Table II²). Furthermore, improvements in pulmonary function, compared to baseline (Table IV²), were consistently higher in the ketotifen-treated group versus the placebo-treated group. These results demonstrate the efficacy of ketotifen in the treatment of pediatric asthma.

In recent years, it has become recognized that airway inflammation contributes to the pathophysiology of asthma³ and that long-term anti-inflammatory therapy should be used to control this component of airway obstruction. The results of this multicenter study² demonstrate that ketotifen can reduce the use of bronchodilator (theophylline) and improve pulmonary function in the treatment of chronic asthma of mild severity.

A. Knight, MD

Division of Clinical Immunology
Sunnybrook Medical Center
Toronto, Canada

G. H. Nickerson, MD
Bridgewater, Canada

D. W. Moote, MD

Department of Clinical Immunology and Allergy
Victoria Hospital
London, Canada

J. P. St-Pierre, MD

Department of Clinical Immunology and Allergy
Ste-Justine Hospital
Montreal, Canada

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In re: Van Bever HP, Stevens WJ. (JACI 1990;86:141-6)

To the Editor:

I am concerned that poor research methodology in this study may have led to erroneous conclusions. In the first year of this study, all patients received immunotherapy, and the investigators observed and concluded that there was an improvement in the late asthmatic reaction (LAR) after allergen challenge. I do not need to belabor the limitations of not having a control group, blinding, and randomization.