

Correspondence

Study design is a major determinant of whether equivalence or superiority is demonstrated

To the Editor:

Clinical studies can be designed to demonstrate differences or equivalence by selecting specific outcome parameters, patient populations, and duration of therapy. One must look to carefully executed and comprehensive meta-analyses to effectively answer a question of superiority of one class of medication over another. *The Cochrane Database of Systemic Reviews* has published a meta-analysis of the comparative inhaled corticosteroid versus leukotriene modifier literature and concluded that the inhaled corticosteroids are superior to leukotriene modifiers for FEV₁ improvement, symptom scores, nighttime awakenings, rescue medication, and rate of exacerbations.¹ The study by Israel et al² differs from many of the studies in this meta-analysis by collecting data in a design methodology selected to demonstrate equivalence. The short duration of the study limits the number of observations, favors medications that reach their maximal effect in days compared with weeks, and thereby reduces the chance of demonstrating a difference. Inhaled corticosteroids continue to have progressive benefits during the first months of therapy. The results of the Israel study contrast with the findings in the study by Malmstrom et al.³ In the 12-week Malmstrom study, beclomethasone was superior to montelukast for peak expiratory flow rates, quality of life, reduced nocturnal awakenings and asthma attacks, increased number of asthma-control days, and decreased number of days with asthma exacerbations ($P < .05$). Israel et al² do not discuss the differences between these 2 articles in their article nor the strengths or limitations imposed by their study design. The differences might be as simple as the duration of the trial and the outcome parameters selected.

Israel et al² emphasize that improvement in measures of lung function might not correlate with symptom control or be the ultimate outcome. They correctly highlight the importance of symptom and exacerbation control. But is this study designed to address disease control? The authors define asthma-control days as having no nighttime awakenings, having no asthma attacks, and using no more than 2 sprays of albuterol a day. In Busse et al,⁴ when studying rescue-free days, a higher level of disease control, there was a 50% greater number of days without rescue albuterol with fluticasone compared with montelukast. It appears that Israel et al might have been more intent on designing a trial that would show equivalence than in designing one to actually determine whether the one treatment was more effective on the basis of a relevant efficacy measure. Because of the short duration of this study, none of the 3 treatment arms had a significant number of exacerbations.

Strunk and Korenblat⁵ write the following in their editorial in the *Journal*: "A drug that both improves symptoms and had continued effects on FEV₁ would be more valuable than either an ICS or an LRA, and such a drug should be sought." The baseline demographics in the study by Israel et al² demonstrate that the patients in this study have moderate persistent asthma by means of National Asthma Education and Prevention Program criteria (FEV₁, 66% to 67% of predicted value; albuterol puffs per day, 5.6-5.8) and warrant combination therapy. Because these patients are untreated, it is not surprising that asthma-control days are low for both active treatments. The recent 2002 Update for the Diagnosis and Management of Asthma by the National Institutes of Health/National Heart, Lung, and Blood Institute recommends that patients with moderate or more severe persistent asthma should receive combination therapy with an inhaled corticosteroid and an inhaled long-acting β_2 -agonist. The important research question is the following: "What is the best therapy for good control of asthma?" rather than "Do these 2 classes of drugs have equivalent efficacy even when their efficacy is poor?" This article does not offer new information on the treatment of asthma but rather demonstrates the importance of study design to achieve predictable outcomes.

Stuart W. Stoloff, MD

Clinical Professor of Family and Community Medicine
University of Nevada School of Medicine
Reno, Nev

David A. Stempel, MD

Clinical Associate Professor of Pediatrics
University of Washington
Seattle, Wash

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To the Editor:

Drs Stempel and Stoloff¹ suggest that our article offers no new insights into the treatment of asthma, that meta-analyses are the preferred method of evaluating