

Editorial

Choice of a medication to treat asthma: Is an improvement in symptoms sufficient for deciding?

Key words: Asthma, treatment

Selection of medications most appropriate to improve both short-term and long-term quality of life remains a major challenge for clinicians caring for patients with asthma. Underlying the choice of medicines for an individual patient is knowledge of the role of inflammation in asthma, the mechanism of action of a medication, the likelihood of patient adherence, and studies of outcomes of medication use. Typical studies of medication effectiveness compare the response to a medicine with the response to a placebo—a necessary comparison, given the possibility of patient and investigator bias in evaluating response to therapy. These studies are essential to give clinicians guidance in medication choice. Studies comparing medicines that are known to be effective are also important. Too few studies done by the pharmaceutical industry accomplish this latter goal.

The article by Israel et al¹ in this issue of the Journal makes such a comparison: it looks at 2 medications known to be effective for asthma, an inhaled corticosteroid (ICS) and a leukotriene receptor antagonist (LRA). This head-to-head comparison is a useful contribution to our management of patients. In their article, the investigators have chosen as their primary outcome days of asthma control. This outcome is obviously relevant to patients and to clinicians who are caring for them. The outcome is clearly defined, relating as it does to need for albuterol, presence of nighttime awakenings, and absence of asthma exacerbations. Associated outcomes of asthma attacks, flare-ups, and sustained control are also clearly defined. The authors find that the percentage of days of asthma control was almost identical for the ICS (beclomethasone) arm and the LRA (montelukast) arm. Montelukast was at least equal to beclomethasone in terms of frequency of asthma attacks, asthma flare-ups, and corticosteroid rescue.

Abbreviations used

CAMP: Childhood Asthma Management Program

ICS: Inhaled corticosteroid

LRA: Leukotriene receptor antagonist

Symptoms and other clinical outcomes are obviously important in medication selection and follow-up of effectiveness, but information concerning the effects of medications on airway function is also important, both for selecting a medication initially and for following its usefulness over the longer term. In the article by Israel et al, beclomethasone had a greater effect than montelukast on improving FEV₁. How are clinicians to use this information in their practice? Whereas patient acceptance of a medication is determined in large part by control of symptoms, for determination of the long-term outcome from asthma—and therefore of the medication's effectiveness—one must consider its effectiveness in improving and maintaining improvement of lung function—specifically, FEV₁.

FEV₁ is a powerful predictor of pulmonary and cardiovascular morbidity and mortality.²⁻⁵ Low levels of FEV₁ are associated with risk even for people without symptoms.⁵ Given the importance of FEV₁ to outcome, it is essential that clinicians take the effect on FEV₁ into consideration when choosing a medication and then following its value. However, with respect to FEV₁, the increased benefit of ICSs in comparison with LRAs is complicated. There are numerous studies demonstrating beneficial effects of ICSs on FEV₁ over the short term (weeks to months). However, when patients are followed over a longer term, such as in the Childhood Asthma Management Program (CAMP), in which outcomes are determined over a 3.5- to 5.5-year interval, it is not clear what impact ICSs have on lung function over such a long period. In CAMP, patients on ICSs had an increase in FEV₁ in the first 3 or 6 months of therapy, but by the end of the long-term study there was no difference between placebo and ICS groups for the primary outcome of post-bronchodilator FEV₁.⁶ However, ICS use in CAMP improved airway reactivity to methacholine throughout the entire period of follow-up, even though the effect on FEV₁ was not maintained.⁶ In addition, use of ICSs in CAMP did improve multiple clinical outcomes to a significant degree.⁶ The clinician must interpret the results of CAMP to indicate that ICSs do have a beneficial effect in the treatment of asthma, regardless of the lack of impact on FEV₁ at the end of the prolonged treatment

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interval. The information presented by Israel et al might be interpreted from the same viewpoint in helping with medication selection.

The finding of equal control of symptoms produced by an ICS and an LRA is useful information for clinicians. However, in using the results of this study in modifying practice, the reader must consider other reports in the literature and the design of the current study. As pointed out by the authors, the results of their work are in contrast to what was found in a similar study comparing low-dose fluticasone with montelukast. In that study, FEV₁ improved more with fluticasone than with montelukast—a finding consistent with the current results. However, unlike what was seen in the current investigation, fluticasone had a greater effect on β -agonist use, symptoms, and rescue-free days. Israel et al indicate that the differences between the fluticasone/montelukast and beclomethasone/montelukast comparisons might be related to the use and dose of fluticasone, the length of the study, or differences in compliance between the different drug preparations across the studies. Given these possibilities, the reader must consider the value of a comparison between beclomethasone as the ICS and montelukast. Can one conclude that LRAs are equivalent to ICSs in improving symptoms, or are the results related merely to the selection of beclomethasone, an ICS known to be less potent than fluticasone, as the ICS for study?

There are several issues pertaining to the design of the current study that also must be considered. The lack of a uniform approach in the delivery of the beclomethasone (use of a spacer being permitted but not required) might have decreased the effectiveness in the ICS arm. In addition, measurement of adherence by patient recall of inhaler use at the last study visit does not allow analysis of drug use as a possible modifier of the results. The authors suggest that compliance with an inhaler might be worse than compliance with a tablet when such compliance is not enforced. This response is often put forward as a reason to use LRAs, and it has some support. Not collecting adherence data limits our ability to consider the possibility that the equivalence of beclomethasone and montelukast simply reflects the fact that beclomethasone was not used as completely as montelukast.

This article raises still other issues that must be considered. Given the patients selected for study and the approaches used (monotherapy for patients with moderately severe persistent asthma by study entry criteria), neither drug achieved adequate control, inasmuch as 35% to 40% of subjects had less than 10% of days of asthma control and only 15% to 18% had greater than 90% control. This is an expected outcome. However, selection of patients with this severity does allow comparison of results, because patients with this severity obviously have enough symptoms for improvements from medication to be observed. The finding that differences from baseline were achieved for both groups is a not-unexpected outcome, given the numerous studies of both of these drugs in improving asthma control. However, are these patients appropriate subjects for the study

described? Their asthma is clearly too severe for monotherapy, as suggested by the Guidelines.⁷ Furthermore, the authors included a placebo group to ensure a favorable response to the medications being used. One would have to raise the issue of the necessity of a placebo group and thus of the ethicalness of placing patients with moderately severe asthma at risk by giving them placebo, even for a short period of time. Pharmaceutical companies continue to compare responses to medications with responses to placebo rather than using drugs of known effectiveness as the comparison for a new medication. As indicated earlier, placebo-controlled trials have a necessary place in studies of drug effectiveness, but use of placebo must be carefully applied.

Although asthma is a heterogeneous illness, the clinical presentations are well recognized and usually follow a set pattern, thus allowing for a simple classification—mild, moderate, and severe asthma—that is based on chronicity and severity. This classification, first proposed in 1984,⁸ has been used in the recommendations of the National Heart, Lung, and Blood Institute, including the latest version of its guidelines for asthma management.⁷ The listing of goals for asthma control includes both a combination of desired clinical symptom outcomes and objective lung measurements that the clinician should strive to attain. LRAs improve symptoms and are well accepted by patients. ICSs also improve symptoms and in addition have effects on FEV₁, though these effects might be transient. The clinician and researcher must ask whether either drug is optimal for treatment of asthma. A drug that both improves symptoms and has continued effects on FEV₁ would be more valuable than either an ICS or an LRA, and such a drug should be sought. In the meantime, clinicians will choose and patients will accept medications on the basis of improvement in symptoms. The results of the current study can be helpful in such a selection.

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REFERENCES

1. Israel E, Chervinsky PS, Friedman B, van Bavel J, Skalky CS, Ghannam AS, et al. Effects of montelukast and beclomethasone on airway function and asthma control. *J Allergy Clin Immunol* 2002;110:847-54.
2. Sobol B, Herbert S, Emirgil C. The high incidence of pulmonary functional abnormalities in patients with coronary artery disease. *Chest* 1974;65:148-51.
3. Vestbo J, Lange P. Forced expiratory volume in 1 second (FEV₁)—a respiratory physiological measurement of considerable prognostic value [in Danish]. *Ugeskr Laeger* 1991;153:2292-5.
4. Keys A, Aravanis C, Blackburn H, Djordjevic B, Dontas A, Fidanza F, et al. Lung function as a risk factor for coronary heart disease. *Am J Public Health* 1972;62:1506-11.
5. Knuiman M, James A, Divitini M, Ryan G, Bartholomew H, Musk A. Lung function, respiratory symptoms, and mortality: results from the Busselton Health Study. *Ann Epidemiol* 1999;9:297-306.
6. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
7. Expert Panel Report 2: National Heart, Lung, and Blood Institute, National Institutes of Health. Guidelines for the diagnosis and management of asthma. 1997. NIH publication no. 97-4053.
8. Korenblat, P. Asthma management. In: Korenblat P, Wedner H, editors. *Allergy: theory and practice*. Orlando (FL): Grune and Stratton; 1984. p. 309-24.