

Effects of montelukast in patients with persistent asthma using inhaled corticosteroids plus additional second-line therapy

To the Editor:

The retrospective data by Barnes et al¹ succinctly demonstrated that benefits were conferred by the addition of montelukast for real-life patients with asthma. Indeed, 66% of patients—irrespective of disease severity or duration or existing treatment—were observed to have a significant improvement in overall control of asthma after attenuation of the cysteinyl leukotriene pathway.

It is particularly interesting to note that concomitant montelukast provided beneficial effects in patients using inhaled corticosteroids plus additional second-line controller therapy. Despite the fact that concomitant montelukast is advocated in current guidelines,^{2,3} the authors quite correctly point out that there is a paucity of data showing beneficial effects. For example, Robinson et al⁴ failed to demonstrate any additional effects of montelukast on the primary endpoint of peak expiratory flow in patients with asthma using inhaled corticosteroid plus additional therapy (mostly long-acting β_2 -agonists). However, because the patients studied were likely to have been maximally bronchodilated (by the long-acting β_2 -agonist moiety), it is not particularly surprising that such a smooth muscle-dependent outcome was not influenced by the addition of montelukast. In the same study, the short treatment period (14 days) would have also precluded any demonstrable effect on exacerbation frequency. In another randomized, placebo-controlled study, the effect of montelukast in conjunction with fluticasone propionate 500 μ g/d plus salmeterol was examined.⁵ As expected, no further benefit was achieved in terms of airway caliber, although commensurate reductions in airway hyperresponsiveness and inflammatory biomarkers were observed.

It stands to reason, therefore, that the additional beneficial effects of montelukast may in fact occur through its ability to suppress airway hyperresponsiveness and the underlying asthmatic inflammatory pathway. Further data are required to confirm whether this in turn has a positive effect on parameters of airway remodeling. The data by Barnes et al provide clinicians with a timely reminder that the benefits achieved with leukotriene receptor antagonists are indeed to be found across a range of asthmatic phenotypes—even in those at the more severe end of the spectrum.

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The authors of the article were provided with the opportunity to respond to this correspondence from Currie et al. They indicated that they could not add any further information to the correspondence. They agree that further studies are needed in the area of markers of inflammation, lung function, and airway remodeling in asthma to elucidate potential areas of improvement.

REFERENCES

1. Barnes N, Thomas M, Price D, Tate H. The national montelukast survey. *J Allergy Clin Immunol* 2005;115:47-54.
2. British guideline on the management of asthma. *Thorax* 2003;58(suppl 1):i1-i94.
3. GINA Workshop Report, Global Strategy for Asthma Management and Prevention—updated 2004: scientific information and recommendations for asthma programs. National Institutes of Health publication number 02-3659. Available at: <http://www.ginasthma.com>.
4. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet* 2001;357:2007-11.
5. Currie GP, Lee DK, Haggart K, Bates CE, Lipworth BJ. Effects of montelukast on surrogate inflammatory markers in corticosteroid-treated patients with asthma. *Am J Respir Crit Care Med* 2003;167:1232-8.

Available online April 25, 2005.
doi:10.1016/j.jaci.2005.03.005

Response to Wolfe and Marks

To the Editor:

Dr Wolf and Mr Marks present an argument for increased use of pharmaceutical samples within 2 settings: the clinical office and through tithing to an outside pharmacy serving indigent patients.¹ They acknowledge that dispensing of drug samples is primarily a marketing and drug promotion tool by the pharmaceutical industry. It is important to stress that pharmaceutical samples priced at average wholesale acquisition cost are the single largest form of product promotion for the pharmaceutical industry. The estimate of \$400,000 for a busy 3-person allergy practice seems about right and shockingly large for those unfamiliar with the extent of sampling in asthma specialty practices. Asthma and allergy medications are among the top category of drug class for which samples were given.²

The use of pharmaceutical samples in the office setting does change physician prescribing patterns.^{3,4} Of physicians who dispensed samples, between 49% and 95% dispensed a drug sample that differed from their preferred drug choice. Industry supplies samples for the drugs they are promoting, and samples are not usually supplied for nonbranded products.

In addition, the routine use of samples in the office setting bypasses the pharmacist. The amount of education and instruction associated with the dispensing of samples

is limited and primarily focused on dosing; little to no attention is given to how and when the medication should be taken with meals and drug interactions.² If physicians are going to dispense samples, they must also take on the responsibility of fully educating the patients about their use.

Finally, we must also consider the long-term effect on our patients. Samples will be available for branded, newer, more expensive medications. If this is the most appropriate medication, samples might be a reasonable way to assess the efficacy and tolerance of a new medication in an individual patient. However, this must be done with the knowledge that when we can no longer supply the patient with samples of that medication, they might be left with a more expensive long-term treatment plan.

Alternatively, Dr Wolf suggests a percentage of the pharmaceutical samples be tithed to pharmacies that serve indigent populations. Advantages of this option include the availability of a pharmacist to help with the education and instruction of the patient and more efficient tracking of dispensed samples, as required by law. However, is it in the best interests of our indigent patients to switch medications according to availability? What will be the effect on the overall health of our indigent patients if we repeatedly switch their medication regimen on the basis of the availability of samples. Will there be effects on compliance, patient knowledge, and understanding of their medications and potential side effects? Furthermore, pharmacies that supply samples to patients will need to keep samples separate from retail inventory to avoid possible diversion.

Although the use of samples in the office setting might be an appropriate choice for a given patient, we must be aware that the decision of which drug to use is influenced by which samples are available. The difficulty in remaining unbiased in our choice of therapy has contributed to many large multispecialty group practices to remove samples from their practices. Boltri et al³ compared 2 time periods: January through February 1997, when drug samples were available, and January through February 1998, when sample distribution was prohibited. They observed that after the prohibition of sample distribution, there was an increase in first-line antihypertensive use from 38% to 61%. Similarly, the use of samples through a tithing program to outside pharmacies will also influence the medication prescribed for our indigent patients. Ideally, we should prescribe a medication for a patient on the basis of our perception of what is the best drug for the overall clinical situation. However, reality dictates that the economics of these decisions also have to be considered. Prescription drugs account for only 11% of medical costs but an increasingly large share of out-of-pocket costs to patients.⁵ How and where pharmaceutical samples are incorporated into this decision process needs to be carefully considered.

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Editor's note: The authors of the article to which this Correspondence refers elected not to provide a reply to it for publication.

REFERENCES

1. Wolf BL, Marks A. Largess, excess, and tithing. *J Allergy Clin Immunol* 2005;115:1320-1.
2. Backer EL, Lebsack JA, Van Tonder RJ, Crabtree BF. The value of pharmaceutical representative visits and medication samples in community-based family practice. *J Fam Pract* 2000;49:811-6.
3. Boltri JM, Gordon ER, Vogel RL. Effect of antihypertensive samples on physician prescribing patterns. *Fam Med* 2002;34:729-31.
4. Chew LD, O'Young TS, Hazlet TK, Bradley KA, Maynard C, Lessler DS. A physician survey of the effect of drug sample availability on physicians' behavior. *J Gen Intern Med* 2000;15:478-83.
5. Smith C, Cowan C, Sensenig A, Caitlin A. Health Accounts Team. Health spending growth slows in 2003. *Health Aff (Millwood)* 2005;24:185-94.

Available online June 1, 2005.
doi:10.1016/j.jaci.2005.03.050

Atopy and asthma: An epidemic of unknown cause

To the Editor:

In the Detroit Children's asthma study, the number of cases of asthma that have developed by the age of 5 to 7 years is too small to draw most conclusions.¹ The authors recognize this but have published their finding that fathers with continuing symptoms present a greater asthma risk for their children. They conclude that persistent symptoms indicate a stronger genetic susceptibility. Had they considered it possible that atopy might be caused by a transmissible agent, they could have concluded that a symptomatic parent might be more contagious.

The specific abnormal T_H2 clones responsible for driving atopy not only have become immortal but also produce less IL-10 than normal T_H2 cells in the same subject. Once boosted to a manifested level, these cells remain active for years, even in the absence of further allergen exposure. The cause of the abnormal specific clones is unknown. Some viruses immortalize T_H2 clones to preserve themselves and avoid the host's immune defenses (eg, herpes simplex virus and human T-cell leukemia virus 1). Atopy susceptibility is reduced by half in subjects with antibody to hepatitis A and an insert at Tim1 (an area where viral uncoating and entry are facilitated).² In view of the current epidemic of atopic disease, epidemiologists must consider every possibility.

It is also important for epidemiologists to know that it is normal to make IgE to some things. All positive skin test results, especially to mites, which after all are parasites, are not signs of atopy. They may indicate only current exposure. (For example, positive skin test results to mites were common in rural Ethiopia, where asthma was rare.)

Susceptibility of the very young with widespread immunity in adults is a common pattern in many infectious