
Correspondence

To the Editor:

I am very pleased to see that an attempt has been made to critically evaluate the role of leukotriene receptor antagonists (LTRAs) in seasonal allergic rhinitis.¹ It is crucial that any new therapeutic option to treat allergic disease be evaluated carefully to gain additional perspective as to the potential benefits and limitations each therapy provides to practitioners and, most importantly, patients.

I believe, however, that evaluation of any given therapy to treat allergic disease must take a multifactorial approach. Clinical trials, which evaluate multiple endpoints, including but not limited to US Food and Drug Administration (FDA)-mandated endpoints, the impact of compliance and adherence, the systemic modulation of allergic disease, and a practitioner's clinical experience via "real-world efficacy" studies incorporate efficacy. Although the rational approach Dr. Nathan¹ uses provides value, the evaluation is limited in its scope, with substantial conclusions being drawn on incomplete data. The data available and the biases of the studies cited limit the generalizability of his conclusions.

Although the paper possesses errors (ie, referring to leukotrienes as cytokines, references that incorrectly label the use of therapy²), I would prefer to attribute those errors to the short editorial turnaround time of 2 days. My main concerns lie in the conclusions drawn from various different types of clinical trials listed in the paper and the absence of consideration of a multifactorial evaluation of therapy.

The FDA, as well as most investigators, recognizes the inherent variability and difficulty of conducting allergic rhinitis studies because of the subjective nature of endpoints, pollen variability that may skew results, etc. It is imperative that large, well designed, multicenter trials be conducted to critically evaluate the benefit of any given therapy.³ Decisions regarding therapy must be heavily weighted with studies that take into account the variables listed above. Studies with small patient numbers, a limited number of study centers, or a poor design³⁻¹¹ (9 of the 13 trials referenced in Table 1, pp. 185-186) cannot be given equal weight as large-scale, well designed, multicenter clinical trials.¹²⁻¹⁴ Especially in seasonal allergic rhinitis trials, clinicians should place a large amount of weight on the critical burden of evidence presented to the panel of FDA members and the stringent requirements they have for granting an indication of allergic rhinitis. It is also imperative that we evaluate studies and simultaneously draw conclusions based on the correct patient types presenting with the disease in question. It is of concern that the author refers to Phipatanakul et al¹⁵ to demonstrate that LTRAs do not benefit patients with both upper and lower airway diseases, when the patients in this study only had documented lower airway disease.

As clinicians, we need to ensure that appropriate evaluation of therapy is multifactorial. It is critical in evaluating a therapy to evaluate the impact of compliance and adherence on treatment. As allergic rhinitis poses a significant quality-of-life impact to patients¹⁶⁻¹⁸ and can serve to exacerbate pre-existing conditions such as asthma,¹⁹ therapies that patients will readily use and that can provide them with disease control are of paramount consideration. Since allergic disease is a manifestation of a systemic immune response, we need to understand what systemic effects various therapies may have on other manifestations of the immune response in various target organs. As such, oral agents such as LTRAs need to be evaluated for the entirety of their effect at numerous target organs. We as clinicians also need to evaluate therapy from our clinical perspective and incorporate our experience into any overall efficacy evaluation.

As we move forward in continuing to broaden our understanding of systemic allergic disease, we also need to broaden our frame of reference to make the most informed decision possible. This needs to include the results of clinical trials, the impact on compliance and adherence, our clinical experience, and patient perspective. We must evaluate the studies with the best design and the impact of therapy on the systemic allergic disease process to make the most informed decision.

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Response:

I appreciate the opportunity to respond to Dr. Bukstein's letter to the editor. The purpose of my article was to give a comprehensive review of the currently published literature on the use of leukotriene receptor antagonists in the treatment of allergic rhinitis. I also believed it was appropriate to draw conclusions from the existing data as to whether this new indication for an approved drug offers an advantage or a novel approach to the allergic rhinitis armamentarium in patients with or without asthma. As a review article, it would have been inappropriate and incomplete to exclude what Dr. Bukstein refers to as "studies with small patient numbers, a limited number of study centers, or poor design. . ." since

even the authors of the ". . . large, well designed, multicenter trials" make positive references to these boutique studies.

Dr. Bukstein mentions the importance of including "potential benefits and limitations" in any critical evaluation. In the interest of fair balance, I noted in the conclusion section of my review article that some studies of leukotriene receptor antagonists have shown efficacy for sneezing, nasal itching, and drainage despite these improvements not being expected based on our current knowledge of their mechanism of action.

I agree that, in addition to data from controlled clinical trials on which drug approval is based, physicians often consider their own subjective "real-world" experiences in their evaluation of new therapies. I also agree that there is a need for a "multifactorial approach" in evaluating any therapy, which should include patient quality of life, compliance, and adherence to treatment.

Dr. Bukstein continually refers to the importance of treating "the *systemic* allergic disease process," (*italics mine*) with inference that an oral leukotriene receptor antagonist will enhance adherence compared with topical therapy. I am also not sure if he is proposing that leukotrienes are a central mediator for allergic disease or that the use of an oral anti-leukotriene drug is going to have a greater impact on the systemic nonnasal, nonocular symptoms commonly noted in patients with allergic rhinitis. Patients in the real world come to us for relief of nasal symptoms that are caused by *localized inflammation*, and optimum relief of these symptoms is what improves the quality of life for patients with this disease. Relief of these symptoms is the benchmark for evaluating new and existing therapies for seasonal allergic rhinitis. Patient adherence to therapy gives the best results, but only if the prescribed medication effectively relieves symptoms. In allergic rhinitis, the primary complaint for the majority of patients is nasal congestion (blockage), which may impact sleep quantity and quality and have a profound effect on work and school performance. Therefore, using the best medication to alleviate daytime and nighttime nasal congestion should have the greatest impact in improving patient quality of life.

The recently published study, in the May 2003 issue of *Annals*, by Ratner et al¹ reports the results of a head-to-head comparison of intranasal fluticasone propionate, 200 µg, once daily, with oral montelukast, 10 mg, once daily, for the treatment of seasonal allergic rhinitis. The results of this large randomized, double-blind, double-dummy, placebo-controlled study demonstrated that intranasal fluticasone propionate was consistently superior to montelukast with regard to every efficacy endpoint evaluated, including daytime and nighttime nasal congestion. The implications of this study are discussed in detail in my guest editorial published in the same issue² and lend further support to my conclusion that leukotriene receptor antagonists are less effective than intranasal corticosteroids in the treatment of seasonal allergic rhinitis.

Although the verdict may be out in Dr. Bukstein's mind, I believe the more efficacious drug in randomized controlled trials should remain the initial therapy if physicians are going to practice evidence-based medicine. I agree we still need

studies to evaluate reasons for noncompliance and nonadherence. Finally, improved patient satisfaction, including to prescribed medication, remains a key unmet need in the ongoing treatment of allergic disorders.

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FUNGAL CONTAMINATION AND AIR SAMPLING

To The Editor:

Santilli and Rockwell¹ report results of mold air sampling and health symptoms reported by occupants of 2 elementary schools. They conclude that all schools should have mold air testing performed and that an air level of 1,000 fungal spores/m³ should be used as “the standard for a healthy environment.” No analysis is presented showing that health symptoms reported by school occupants were associated with a particular exposure level. We agree that mold contamination resulting from water intrusion in buildings is a potential health risk to building occupants, and it needs to be evaluated and controlled. However, we would not use air sampling for molds as the method of choice for evaluating mold problems in buildings, and we do not agree that quantitative mold-sampling results are readily interpretable in terms of health risk.

If mold contamination is suspected in a building, the primary approach for evaluating the building is a thorough visual inspection, focusing on locations where water or mold growth has been observed or where odors are prominent. Mold contamination in water-damaged buildings is often readily apparent. Sometimes, minor destructive probing, such as lifting carpeting or wallpaper or opening wall cavities, is required to fully visualize the extent of the contamination. The remedy to indoor mold contamination is to remove the moldy materials and correct the underlying water problems. The fungal species present and their levels in air are generally irrelevant to this process. Indoor air levels for molds can be interpreted relative to concomitant outdoor sampling results to qualitatively identify the presence of an indoor mold source. However, this is usually redundant information that is more easily obtained through visual inspection, as is recommended in standard environmental health guidance.^{2,3}

There is no generally accepted “bright-line” indoor mold level that separates healthy from unhealthy environmental conditions. For example, Rao et al⁴ conducted an exhaustive review of proposed indoor-air standards or guidelines for

fungi and concluded that data were not available to establish a health-based value. Fungal levels higher than 1,000 spores/m³ quoted from Bush and Portnoy⁵ were not originally described as defining unhealthy levels, but rather as levels that “most likely represent indoor fungal contamination.” Outdoor spore levels can actually be much higher than this level⁵ (eg, Figs 5 and 6, pp. 205 and 207 of Santilli and Rockwell¹), and yet many people are unaffected by such exposures. Conversely, mold-sensitized patients may experience symptoms at exposure levels below 1,000 spores/m³.

Volumetric air sampling for fungal spores is a valuable tool for certain applications, such as research studies. However, it generally has little effect on the remedy for indoor mold contamination (ie, remove the moldy materials and fix the water problem). We favor recommendations to allot limited resources for necessary maintenance to prevent water problems in schools and recommendations that encourage building maintenance staff to be more vigilant for signs of water intrusion when it does occur.

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Response:

We thank the authors of the above letter for sharing their expertise on this matter. As they stated, “. . . mold contamination resulting from water intrusion in buildings is a potential health risk to building occupants, and it needs to be evaluated and controlled,” and we are pleased that the New York Department of Health is concerned about this health issue.

We agree with much of what the above authors suggest, and we want to clarify that we do not believe that volumetric air sampling should replace a visual inspection to determine mold contamination. However, we remain strong proponents of volumetric air sampling to *initially* evaluate indoor air

quality in schools, followed by a visual inspection by an environmental expert if contamination is suspected. Relying solely on visual inspection has not proven to be reliable enough.

Indoor mold contamination creates an unsafe environment for mold-sensitive patients, and setting the standard at 1,000 spores/m³, a level that "most likely represent indoor fungal contamination,"¹ gives schools an easily understood metric to evaluate air quality.

Our experience has shown us that schools do not currently have the resources to evaluate potential indoor mold contamination in their classrooms. Some schools have such extensive contamination that we reported volumetric spore counts of more than 50,000 spores/m³ in one classroom.² A visual inspection of that classroom surely would have revealed an extensive mold contamination, but no one looked for many years. If this school had been required to perform volumetric sampling on a regular basis, or even upon the request of a teacher or parent, the contamination would have been found years earlier, and an environmental expert would have been called in to help remediate the problem. Standards that determine possible indoor mold contamination would provide tangible protection for most mold-sensitive students and teachers.

Volumetric air sampling is a cheap and reliable method to provide administrators with a snapshot of their school's indoor air quality. The Allergenco MK-3 air sampler (Allergenco, San Antonio, TX), for example, provides results equal to the Burkard (Burkard, Rickmansworth, Hertfordshire, UK), costs under US\$1,000, and is approximately the size of a lunchbox.² The samples are extremely easy to take, and slides can be read by a variety of experts. Once contamination is suggested, parents, teachers, and administrators can make a case to further evaluate the problem with a visual inspection by an expert.

We welcome environmental experts to this debate to help establish standards to ensure healthy air in our schools.

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To the Editor:

In this excellent study,¹ Dr. Rebecca Gruchalla et al conclude by using the gold standard methacholine challenge that a questionnaire, the International Study of Asthma and Allergies in Childhood (ISAAC), in conjunction with step testing is not adequate as a screening for asthma. They refer to the work by Feinstein et al² using a step test for exercise-induced asthma screening. I would be interested in Dr. Gruchalla's

reaction to the data from Gerald et al,³ who are part of the Feinstein group, published as a multistage asthma screening procedure for elementary schoolchildren in *Journal of Asthma*, in which a questionnaire from the University of Alabama at Birmingham was used to separate students into 3 categories: those with previous asthma, those with suspected asthma, and those with no evidence of asthma. The students who were then classified as having suspected asthma underwent further testing, including spirometry and a step test exercise challenge.

Using the questionnaire alone, the measured asthma prevalence was 32%; with the addition of spirometry and step testing, this reduced the estimate to approximately 10%. Critically, the diagnosis of asthma was confirmed in 96% of children who saw the physician in the study.

The authors concluded that this study procedure, using a step test and questionnaire, could be used to evaluate schoolchildren with suspected undiagnosed asthma. The authors indicate that the limitation of the study is that none of the children who were classified as having no evidence of asthma by questionnaire, spirometry exercise testing, or physician evaluation. Thus, the sensitivity and specificity of the University of Alabama at Birmingham screening protocol still need to be determined. The students were only evaluated as well in an indoor environment.

I recognize, as Dr. Gruchalla points out, that exercise-induced asthma may not be an optimal way to screen for asthma, though it is present in 90% of children with asthma. I would welcome her remarks on the findings of Gerald et al³ that exercise in challenge with step test and questionnaire provides a confirmed diagnosis of asthma in 96% of children who saw the study physician. Gerald et al conclude, in contrast to Dr. Gruchalla's conclusions, that this screening procedure with a questionnaire and step test can be used to identify schoolchildren with suspected but undiagnosed asthma.

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Response:

Thank you for your correspondence regarding our manuscript entitled, "Results of an inner-city school-based asthma and allergy screening pilot study: a combined approach using written questionnaires and step testing."

I read the manuscript by Gerald et al in the *Journal of Asthma* that you referred to in your letter. You are correct in stating that Gerald et al found that asthma was confirmed in 96% of children who saw a study physician. This fact was stated in the abstract. However, in the Results section, more detail is provided. Only children (1) who had previously diagnosed asthma, (2) who had abnormal pulmonary function test results, or (3) who had abnormal step test results were referred to a physician. Thus, only children with known asthma as well as those who had abnormal test results (pulmonary function tests/step tests) were evaluated by a study physician. I am not surprised that 96% of these children were found to have asthma by the physician.

In your letter, you state that, "Gerald et al conclude, in contrast to Dr. Gruchalla's conclusions, that this screening procedure with a questionnaire and step test can be used to identify schoolchildren with suspected but undiagnosed asthma." Actually, this statement is not correct. The findings of Gerald et al are very similar to ours. They found that of 1,414 children who had questionnaire results consistent with suspected asthma, only 73 (5.2%) had positive step test results. We found that 16.7% of children who had suspected asthma (based on questionnaire results) had either positive step test results or reversible airway obstruction at baseline. Thus, both groups found that a minority of children who had suspected asthma from questionnaire data had positive step test results.

Again, thank you for your comments. I hope that I have sufficiently addressed your question.

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CARBOXYMETHYLCELLULOSE ALLERGY AS A CAUSE OF SUSPECTED CORTICOSTEROID ANAPHYLAXIS

To the Editor:

In the February 2003 issue of the *Annals*, Karsh and Yang reported an anaphylactic reaction to intra-articular triamcinolone.¹ The patient was a 75-year-old man who developed syncope, urinary incontinence, and generalized hives 10 minutes after receiving an intra-articular injection of 80 mg of triamcinolone (Kenalog; Westwood-Squibb, Montreal, Quebec, Canada) and 1% carbocaine in the right shoulder. The possible implication of carbocaine was adequately ruled out by a subcutaneous provocation test, and the authors reported allergy to triamcinolone. However, they performed prick tests with dilutions of the commercial preparation Kenalog, which, in fact, contains not only triamcinolone but also benzylalcohol, polysorbate 80, and carboxymethylcellulose. We believe that triamcinolone allergy cannot be confidently diagnosed without carboxymethylcellulose allergy being ruled out.

We report the case of a 48-year-old man who developed severe pruritus, generalized urticaria, dizziness, vomiting, and

loss of consciousness 2 hours after the intra-articular administration of Trigon Depot (triamcinolone, benzylalcohol, Tween 80, and carboxymethylcellulose; Bristol-Myers Squibb, Anagni, Italy). A prick test with the commercial preparation was strongly positive, whereas prick and intradermal skin tests to common commercial preparations of hydrocortisone, methylprednisolone, betamethasone, paramethasone, and dexamethasone were negative. Parenteral administration of 40 mg of methylprednisolone was well tolerated. Prick test with 1 mg/mL carboxymethylcellulose in saline was followed by a strong positive wheal-and-flare local reaction with severe forearm itching and erythema lasting 30 minutes. Saline carboxymethylcellulose dilutions were prepared and the patient underwent an endpoint prick test that proved positive from 10^{-4} mg/mL. The patient refused further procedures. Prick tests to Trigon Depot and carboxymethylcellulose, 1 mg/mL, performed in 6 controls were negative.

Carboxymethylcellulose was identified as the causative allergen in 2 anaphylactic reactions after administration of triamcinolone,² barium sulfate suspension,³ and in 2 additional cases of immediate hypersensitivity reactions to parenteral corticosteroids.⁴ Recently, carboxymethylcellulose has also been identified as the responsible allergen in a patient with acute urticaria after Trigon Depot administration. In this case, triamcinolone allergy was ruled out by negative prick test and simple blind provocation with isolated triamcinolone.⁵

Carboxymethylcellulose (also called carmellose) is a component of several drugs, mainly depot preparations, syrups, and diagnostic suspensions. Thus, a detailed workup must be made to rule out this dangerous additive allergy when a carboxymethylcellulose-containing drug reaction is suspected.

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