

Cystic fibrosis gene mutations and chronic rhinosinusitis

To the Editor:

In their review of the definition, pathophysiology, treatment of rhinosinusitis by Meltzer et al,¹ there is no discussion of the association between mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and chronic rhinosinusitis.² Most of these patients do not meet diagnostic criteria for cystic fibrosis because their sweat chloride is not elevated above 60 mmol/L and they do not have evidence of 2 disease-causing *CFTR* gene mutations. However, some of the patients with *CFTR* gene mutations and chronic rhinosinusitis reported by Wang et al² did have other features of cystic fibrosis, such as infertility and infection with *Pseudomonas aeruginosa*. Identification of *CFTR* gene mutations in patient with chronic rhinosinusitis may potentially be of clinical importance in the future, because pharmacologic therapies to overcome defective *CFTR* function are under development.³

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Editor's note: This Correspondence has no accompanying reply. The authors of the Meltzer article chose not to reply, saying that the correspondence provides interesting information and is worthy of publication.

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Leukotriene receptor antagonists are not as effective as intranasal corticosteroids for managing nighttime symptoms of allergic rhinitis

To the Editor:

I wish to comment on the supplement published in the November 2004 issue titled "Allergic Rhinitis After Hours: The Relevance and Consequences of Nighttime Symptoms."¹ Nasal congestion associated with allergic rhinitis was identified as an important risk factor for sleep-disordered breathing, sleep fragmentation, daytime

somnolence, and fatigue, and it was noted that nasal congestion and other rhinitis symptoms follow a circadian rhythm, being more severe at night and early in the morning. Chronotherapy, the timed dosing of rhinitis medications to manage optimally the diurnal variation in nasal congestion and other rhinitis symptoms, was discussed, as well as the advantages and disadvantages of each medication class in relation to nighttime rhinitis symptoms; however, readers must draw their own conclusions regarding the most effective medication class.

Three large, double-blind, randomized, placebo-controlled trials of montelukast 10 mg (MON), the only leukotriene receptor antagonist approved in the United States for seasonal allergic rhinitis, were discussed in the supplement.²⁻⁴ Compared with placebo, MON administered once daily at bedtime significantly reduced the nighttime symptom scores and peripheral blood eosinophil counts in all 3 trials.

However, in contrast with the 3 large trials cited for montelukast, the intranasal corticosteroid trials discussed varied considerably in size, scope, and design. The supplement did not include a discussion of a recent large, randomized, double-blind, double-dummy, parallel-group trial in 705 subjects with seasonal allergic rhinitis that compared the effectiveness of a 15-day course of intranasal fluticasone propionate aqueous nasal spray 200 µg (FPANS) with MON, both administered once daily in the evening.⁵ The results of this study showed that FPANS was consistently superior to MON for all daytime and nighttime symptoms, including nasal congestion. The nighttime symptoms (difficulty going to sleep, nighttime awakenings, nasal congestion on awakening) and scoring in this trial were the same as in the 3 montelukast trials cited. In addition, a randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial in 62 subjects with seasonal allergic rhinitis compared subjects treated with FPANS, MON, MON + loratadine 10 mg (LOR), or placebo throughout the grass pollen season.⁶ Subjects assessed their rhinitis symptoms during the study and also underwent nasal biopsy before and during the season for evaluation of local eosinophilic inflammation. Both MON and MON + LOR were less effective than FPANS for control of daytime and nighttime symptoms, including nasal blockage, and for reduction of pollen-induced nasal eosinophilic inflammation on biopsy.

Furthermore, when evaluating nighttime rhinitis treatment options, another important consideration is that many patients with rhinitis have mixed rhinitis, which may include a combination of seasonal allergic, perennial allergic, or perennial nonallergic rhinitis. Whereas MON is currently indicated only for relief of seasonal allergic rhinitis, FPANS is indicated for the management of nasal symptoms of all 3 of these types of rhinitis.

I agree with the premise that therapy aimed at reducing nighttime nasal congestion is paramount for improving

sleep and quality of life, but also that the most effective class of medication (ie, intranasal steroids) should be considered as initial therapy for relief of nighttime rhinitis symptoms.

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Editor's note: This Correspondence has no accompanying reply.

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Efficacy of ant venom immunotherapy and whole body extracts

To the Editor:

Golden¹ presents a useful review of insect venom immunotherapy, but we disagree with his conclusion that imported fire ant (IFA) whole body extract (WBE) has been proven efficacious. Golden¹ stresses the need to understand the natural history of sting allergy and the importance of controlled studies. We add to this the need for prospective design, adequate randomization, and double-blinding.

No prospective controlled study of IFA WBE treatment efficacy or prospective study of the natural history of IFA allergy has been published. Retrospective studies have selection bias, and the natural history of allergy can vary enormously between species. Large prospective studies have found reaction rates on re-exposure to range from 70% for the jack jumper ant through 50% for the honeybee and to 25% for the yellow jacket.^{2,3} Individuals allergic to IFA who react to multiple simultaneous stings (as often occurs) may experience few reactions when exposed to smaller doses of venom.

Our randomized, double-blind, placebo-controlled trial of venom immunotherapy (VIT) provides a model that could be used to assess IFA WBE.³ How did we justify our study, and why did 2 respected university ethics committees approve? First, large studies that have demonstrated the safety of sting challenges after applying health and age exclusion criteria included a total of 238 patients with severe (Mueller grade IV) allergy. Second, the efficacy data from 2 controlled trials of VIT to prevent honey bee and vespid sting anaphylaxis are suboptimal by contemporary standards. One allocated treatment according to patient choice, with outcomes determined by reactions occurring outside hospital that were unobserved by the investigators. The other was single-blind and stratified by using factors that do not influence reaction risk. Finally, the efficacy of immunotherapy varies between species, and we could not be sure of the efficacy of jack jumper ant VIT.

Without double-blinding, investigators can be misled by personal bias and subjective features such as itch, mild flushing, breathlessness, anxiety, and hypotension associated with bradycardia and anxiety. It is notable that we gave epinephrine to a patient who appeared to have a moderate reaction to an injection that was later revealed to be placebo.³

The inclusion of a blind placebo group is the only way to be certain that a sting challenge adequately tests treatment efficacy. This is an important ethical issue; we have observed the death of a man who believed he was protected by ant WBE, reinforcing the risks of a flawed evidence base. As explained, the exposure to a small number of IFA in a sting challenge may be insufficient to provoke anaphylaxis in many people with allergy. Furthermore, insect handling procedures may lead to a depletion of venom as assessed at the time of venom sac dissection.³

Imported fire ant WBE may be an effective treatment, because extracts contain venom proteins and quality control methods have been developed. However, uncertainties remain with regard to the natural history of IFA allergy and whether the dose of venom delivered by IFA WBE extracts is sufficient to confer protection.

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