

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.

## REFERENCES

1. Meltzer EO, editor. Allergic rhinitis after hours: the relevance and consequence of nighttime symptoms. *J Allergy Clin Immunol* 2004;114:S133-53.
2. Philip G, Malmstrom K, Hampel FC, Weinstein SF, LaForce CF, Ratner PH, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002;32:1020-8.
3. Nayak AS, Philip G, Lu S, Malice M-P, Reiss TF. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol* 2002;88:592-600.
4. van Adelsberg J, Phillip G, LaForce CF, Weinstein SF, Menten J, Malice M-P, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003;90:214-22.
5. Ratner PH, Howland WC, Arastu R, Philpot EE, Klein KC, Baidoo CA, et al. Fluticasone propionate aqueous nasal spray provided greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. *Ann Allergy Asthma Immunol* 2003;90:536-42.
6. Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002;109:949-55.

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## Efficacy of ant venom immunotherapy and whole body extracts

*To the Editor:*

Golden<sup>1</sup> 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. Golden<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>3</sup> 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.<sup>3</sup>

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.<sup>3</sup>

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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## REFERENCES

1. Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005;115:439-47.
2. Brown SGA, Franks RW, Baldo BA, Heddle RJ. Prevalence, severity, and natural history of jack jumper ant venom allergy in Tasmania. *J Allergy Clin Immunol* 2003;111:187-92.
3. Brown SGA, Wiese MD, Blackman KE, Heddle RJ. Ant venom immunotherapy: a double-blind, placebo-controlled, crossover trial. *Lancet* 2003;361:1001-6.

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## Reply

To the Editor:

I appreciate the comments of Brown et al.<sup>1</sup> It was clearly only by unintended oversight that the exemplary work of the authors was not cited in my review that focused on treatment strategies in the United States.<sup>2</sup> Their work on the natural history of ant venom allergy and their controlled trial of ant venom immunotherapy are a model to which we should aspire.<sup>3,4</sup> In contrast, there has been no controlled trial of imported fire ant (IFA) whole body extract (WBE) immunotherapy, and the natural history of IFA allergy is unknown.

I am dismayed that my statements were construed to imply that IFA WBE has been proven efficacious. Comparison of IFA WBE and venom *in vitro* and by skin test suggests that although inferior to the venom, WBE contains sufficient allergen to provide reasonable diagnostic accuracy.<sup>5-8</sup> For this reason, I stated, "For fire ant allergy, venom is the most accurate diagnostic material, but WBE have shown adequate diagnostic sensitivity." My statement that "Fire ant immunotherapy is performed with WBE that contains sufficient venom allergens to provide reasonable clinical protection" was based on the reported content of venom allergens in IFA WBE. I did not state that WBE was as potent as venom.<sup>8</sup> The report of clinical efficacy of IFA WBE by Freeman et al<sup>9</sup> had the strengths of prospective sting challenge (instead of retrospective field sting reports) and a limited (but highly significant) control group. Still, Freeman et al<sup>9</sup> concluded that "A controlled prospective trial of WBE versus placebo is needed...to help define the natural history of IFA hypersensitivity." Of recent interest are reports of rush immunotherapy with IFA WBE to prevent systemic and large local reactions, but these too were uncontrolled.<sup>10,11</sup>

Together, the *in vivo* and *in vitro* evidence led to the belief that unlike the other *Hymenoptera*, IFA WBE does

contain sufficient venom allergens to have acceptable, albeit suboptimal, efficacy. Also, unlike the winged *Hymenoptera* WBE, there are relatively few reports of treatment failure with IFA WBE, and no fatalities. Brown et al<sup>1</sup> mention a fatal reaction but not the species of WBE used for treatment or the dose, schedule, and duration of treatment. However, our experience with the winged *Hymenoptera* WBEs "demonstrates the value of a complete understanding of the natural history of the disease in determining the efficacy and indications for treatment and the importance of clinical trials."<sup>2</sup> As Brown et al<sup>1</sup> point out, prospective design and blind treatment are also critical to the strength of the evidence.

The lack of IFA venom products for diagnosis and immunotherapy in the United States is a continuing gap in our repertoire. It is not the ethics but the economics of clinical trials that has deterred the performance of double-blind, placebo-controlled clinical trials of IFA WBE and venom products and encouraged the acceptance of the WBEs as the only option in practice. However, the dilemma posed by the authors has attracted the attention of the Insect Committee of the American Academy of Allergy, Asthma and Immunology, who have now resolved to explore the development of a controlled trial of IFA WBE immunotherapy. (Nelson, personal communication, March 2005). When the efficacy of current treatment has not been proven up to current standards and the risk of treatment failure is a life-threatening reaction, a controlled trial is clearly justified. Our thanks to Brown et al<sup>1</sup> for exposing this important issue.

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## REFERENCES

1. Brown SGA, Heddle RJ, Wiese MD, Blackman KE. Efficacy of ant venom immunotherapy and whole body extracts. *J Allergy Clin Immunol* 2005;116:464-5.
2. Golden DBK. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005;115:439-47.
3. Brown SG, Franks RW, Baldo BA, Heddle RJ. Prevalence, severity and natural history of jack jumper ant venom allergy in Tasmania. *J Allergy Clin Immunol* 2003;111:187-92.
4. Brown SG, Wiese MD, Blackman KE, Heddle RJ. Ant venom immunotherapy: a double-blind placebo-controlled crossover trial. *Lancet* 2003;361:1001-6.
5. Strom GB, Boswell MD, Jacobs RL. In vivo and in vitro comparison of fire ant venom and fire ant whole body extract. *J Allergy Clin Immunol* 1983;72:46-53.
6. Paull BR, Coghlan TH, Vinson SB. Fire ant venom hypersensitivity. I: comparison of fire ant venom and whole body extract in the diagnosis of fire ant allergy. *J Allergy Clin Immunol* 1983;71:448-53.
7. Butcher BT, deShazo RD, Ortiz AA, Reed MA. Superiority of *Solenopsis invicta* venom to whole body extract in RAST for diagnosis of imported fire ant allergy. *Int Arch Allergy Appl Immunol* 1988;85:458-61.
8. Hoffman DR, Jacobson RS, Schmidt M, Smith AM. Allergens in *Hymenoptera* venoms, XXIII: venom content of imported fire ant whole body extracts. *Ann Allergy* 1991;66:29-31.