

CORRESPONDENCE



Immunotherapy with a Ragweed Vaccine

TO THE EDITOR: Creticos et al. (Oct. 5 issue)¹ describe the results of a study comparing a vaccine — consisting of an immunostimulatory DNA sequence conjugated to Amb a 1, a ragweed-pollen antigen — with saline placebo. The study showed improvement of several end points of nasal allergen challenge in the group receiving the Amb a 1-immunostimulatory oligodeoxyribonucleotide conjugate (AIC) vaccine, as compared with the placebo group. However, we question whether saline is the appropriate comparative agent.

Standardized allergen extracts are known to be effective as immunotherapy for allergic diseases. Dynavax Technologies is developing an inhaled immunostimulatory sequence without a linked allergen for the treatment of another allergic disease, asthma.² Therefore, both the immunostimulatory sequence and the allergen (Amb a 1) could have activity against allergic diseases. Since immunotherapy is an established treatment for allergic diseases, it would be important to compare the efficacy of AIC with that of immunotherapy to determine whether the conjugated product offers any benefit over standard immunotherapy. Ideally, future clinical studies evalu-

ating AIC would include a comparison group of patients receiving allergen immunotherapy.

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The views expressed in this letter are those of the authors and do not necessarily reflect the views or policies of the Food and Drug Administration.

1. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;355:1445-55.

2. Dynavax Technologies. Clinical development programs — asthma. (Accessed December 13, 2006, at <http://www.dynavax.com>.)

TO THE EDITOR: Creticos et al. report improvement in the symptoms of allergic rhinitis, with concomitant changes in skin-test sensitivity and antibody titers. However, changes in cellular immune responses were not definitive.

In a randomized, blinded, phase 1 study involving 19 patients with ragweed allergy, we measured ragweed-specific recall responses in antigen-stimulated primary cultures before and 2 and 16 weeks after six subcutaneous injections of either an Amb a 1 immunostimulatory DNA vaccine or placebo. We found that in vivo ragweed-specific responses by type 2 helper T (Th2) cells were selectively redirected toward balanced responses in parallel with increased activity by type 1 helper T (Th1) cells.¹ There were significant decreases in levels of interleukin-5 and CC chemokine ligands 17 and 22 (CCL17 and CCL22, respectively) at 2 and 16 weeks in vaccine-treated patients, accompanied by transient increases in levels of interferon- γ and CXC ligands 9 and 10 (CXCL9 and CXCL10, respec-

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tively). Unrelated (streptokinase) responses and global (phytohemagglutinin) responses were not altered.

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1. Simons FER, Shikishima Y, Van Nest G, Eiden JJ, HayGlass KT. Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA. *J Allergy Clin Immunol* 2004;113:1144-51.

THE AUTHORS REPLY: Seymour and Chowdhury question whether saline is the appropriate comparative agent in trials of allergen immunotherapy. Saline is a recognized control for clinical trials with standard immunotherapy, and it has been used in various clinical trials approved by the Food and Drug Administration's Center for Biologics Evaluation and Research.^{1,2}

At the time we designed our study, it was important to show the efficacy of a study drug as compared with placebo and to provide proof-of-concept and to demonstrate safety. Now that a clear-cut therapeutic response has been shown with a six-injection regimen of AIC, a comparative trial may be justified. A proper study design will nevertheless be difficult to achieve. Standard immunotherapy cannot be safely escalated to the optimal therapeutic dose in six injections and, furthermore, must be continued for at least

3 years. A double-blind, double-dummy design — with one regimen of 6 injections and another regimen of 25 escalating injections with a known risk of anaphylactic reactions, followed by 3 years of maintenance injections — has inherent problems with maintaining proper blinding.

With regard to the comments of Simons and HayGlass concerning their study of AIC in patients with ragweed allergy: because of space constraints, some references and discussion were edited from our original article, including the results of their study³ and of a study by Tulic et al.⁴

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1. Norman PS, Lichtenstein LM, Kagey-Sobotka A, Marsh DG. Controlled evaluation of allergoid in the immunotherapy of ragweed hay fever. *J Allergy Clin Immunol* 1982;70:248-60.
2. Norman PS, Ohman JL Jr, Long AA, et al. Treatment of cat allergy with T-cell reactive peptides. *Am J Respir Crit Care Med* 1996;154:1623-8.
3. Simons FER, Shikishima Y, Van Nest G, Eiden JJ, HayGlass KT. Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA. *J Allergy Clin Immunol* 2004;113:1144-51.
4. Tulic MK, Fiset P, Christodoulouopoulos P, et al. Amb a 1 immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J Allergy Clin Immunol* 2004;113:235-41.

Transmission of Human Herpesvirus 8 by Blood Transfusion

TO THE EDITOR: Hladik and colleagues (Sept. 28 issue)¹ provide evidence of human herpesvirus 8 (HHV-8) transmission by blood transfusion. They suggest that HHV-8 blood screening for immunocompromised patients may be warranted. However, their statement that nucleic acid testing would not be effective for blood-bank screening is debatable. The viral load is an important marker of disease activity for a number of viruses, including the human immunodeficiency virus (HIV), cytomegalovirus, and HHV-8. By contrast, the clinical significance of seroreactivity to HHV-8 antigens is not clear.² Reliable techniques to detect HHV-8 DNA have been developed.² One would expect patients with HHV-8 DNA that is detectable in blood to be at the highest risk for spreading the infection.

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1. Hladik W, Dollard SC, Mermin J, et al. Transmission of human herpesvirus 8 by blood transfusion. *N Engl J Med* 2006;355:1331-8.
2. Tedeschi R, Enbom M, Bidoli E, Linde A, De Paoli P, Dillner J. Viral load of human herpesvirus 8 in peripheral blood of human immunodeficiency virus-infected patients with Kaposi's sarcoma. *J Clin Microbiol* 2001;39:4269-73.