

References

1. Bousquet J, Lockey R, Malling H. Allergen immunotherapy: therapeutic vaccines for allergic diseases. WHO Position Paper. *Allergy* 1998; 53(Suppl. 54).
2. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. ARIA. WHO Initiative. *J Allergy Clin Immunol* 2001;108:S147–S334.
3. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, Mathur AK, Cowley HC, Chung KF, Djukanovic JR, *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. *Lancet* 2000; 356:2144–2148.
4. Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;102:157–164.
5. Wilson DR, Nouri-Aria KT, Walker SM, Pajno GB, O'Brien F, Jacobson MR, Mackay IS, Durham SR. Grass pollen immunotherapy: symptomatic improvement correlates with reductions in eosinophils and IL-5 mRNA expression in the nasal mucosa during the pollen season. *J Allergy Clin Immunol* 2001;107:971–976.
6. Naclerio RM, Proud D, Moylan B, Balcer S, Freidhoff L, Kagey-Sobotka A, Lichtenstein LM, Creticos PS, Hamilton RG, Norman PS. A double-blind study of the discontinuation of ragweed immunotherapy. *J Allergy Clin Immunol* 1997;100:293–300.
7. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *Br Med J* 1999;318:593–596.
8. Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. *Allergy* 1999;54:1022–1041.
9. Adkinson N Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert CL, *et al.* A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324–331.
10. National Institutes of Health, National Heart, Lung, and Blood Institute. WHO/NHLBI workshop report: Global strategy for asthma management and prevention. Publication number 95-3659. Bethesda, MD: WHO; January 1995.
11. Barnes P. Is there a role for immunotherapy in the treatment of asthma? No. *Am J Respir Crit Care Med* 1996;154:1227–1228.
12. Norman P. Is there a role for immunotherapy in the treatment of asthma? Yes. *Am J Respir Crit Care Med* 1996;154:1225–1228.
13. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;16:802–807.
14. Bateman ED, Bousquet J, Braunstein GL. Is overall asthma control being achieved? A hypothesis-generating study. *Eur Respir J* 2001;17: 589–595.
15. Adkinson NF Jr. Immunotherapy for allergic rhinitis. *N Engl J Med* 1999;341:522–524.
16. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87–93.
17. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468–475.
18. Jacobsen L, Dreborg S, Møller C, Valovirta E, Wahn U, Niggemann B. Immunotherapy as a preventive treatment (abstract). *J Allergy Clin Immunol* 1996;97:232.
19. Des-Roches A, Paradis L, Ménardo J-L, Bouges S, Daurès J-P, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99:450–453.
20. Pajno G, Barbero G, De-Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mites by specific immunotherapy. *Clin Exp Allergy* 2001;31:1392–1397.

Immunotherapy Is Not Clinically Indicated in the Management of Allergic Asthma

When immunotherapy was introduced by Noon in 1911 and for most of the 50 years that followed, it was about the only game in town. Not so in the new millennium. To be clinically indicated today, immunotherapy for asthma must be more effective or less toxic, or both, than alternative therapies. Or it must possess some unique advantages that can't be found elsewhere. This is the burden of proof to which I hold my worthy opponent.

So, how effective is immunotherapy, and compared with what? If you look at modern clinical trials of immunotherapy, where symptom indices, pulmonary function, and medication requirements were carefully monitored, the size of the therapeutic effect, if observed at all, is invariably modest (1, 2) and quantitatively comparable to effects observed with any of a number of bronchodilators (3) and cromolyn-like drugs (4).

One illustrative example of this is the collaborative study of immunotherapy for ragweed asthma (5). This careful study observed patients for asthma flares during one ragweed season followed by randomization to high-dose ragweed injections or placebo for the next two years. Morning peak flow measurements during the ragweed season after one year of treatment improved 5.1% ($p = 0.06$); symptom scores did not change, although medication use declined significantly ($p = 0.01$). After two years of treatment the results were even more modest. Numerous clinical studies have documented comparable degrees of effectiveness for drugs such as anti-leukotrienes, salmeterol, and nedocromil.

No published studies have demonstrated a steroid-sparing effect for allergen immunotherapy. A randomized study of perennial allergic asthma in children done at Johns Hopkins showed no difference in the requirement for either inhaled or oral steroids between immunotherapy and placebo groups (6). A di-

rect comparison of inhaled steroids and immunotherapy has not been done, and is not likely to be done because of ethical and logistic constraints. So my first conclusion is that immunotherapy, although effective in model systems, produces modest clinical benefits comparable to what is readily achieved with bronchodilators and nonsteroidal antiallergy drugs.

The next issue is safety. Review of available data through 1992 has indicated that at least three to five individuals die as a result of immunotherapy mishaps each year in the United States (7). The British experience suggests that about 75% of immunotherapy deaths occur in patients with asthma (8), indicating that asthma is a strong risk factor for a fatal outcome from systemic reactions. This observation has led to guidelines that mandate prescreening subjects with asthma before immunotherapy injections.

I am sure that almost all qualified allergy specialists adhere to these guidelines, but the real world is a bit different. Injections are not always under the direct supervision of a qualified specialist, and dosing errors, which are responsible for as many as half of systemic reactions to immunotherapy, can be minimized but probably not eliminated. On the other hand, alternative pharmacotherapies, including inhaled steroids, have remarkably little acute toxicity, and no directly attributable mortality.

Immunotherapy could be clinically indicated in allergic asthma if it possessed advantages or benefits not obtainable with alternative treatments. Immunologic specificity is a distinctive feature of immunotherapy but such specificity is a double-edged sword. If important treatment allergens are omitted the clinical result will be suboptimal. And unlike pharmacotherapy, immunotherapy provides no protection against nonallergic asthma triggers such as viral infections, irritants, and exercise.

Some have suggested that compliance with immunotherapy injections every two to four weeks may be easier to achieve than daily compliance with medication. But in practice, for perennial asthma, it is rarely if ever an either-or proposition. Most perennial asthmatics are asked to do both (9). Some have calculated the cost of supervised immunotherapy to be approximately equal to the cost of daily inhaled steroids (5). Thus, there is no special advantage here.

We all know that moderate doses of inhaled steroids predictably dampen nonspecific bronchial hyperreactivity to a modest degree. With one or two exceptions, studies of immunotherapy, including our own (6), showed no effect on bronchial sensitivity to methacholine or histamine (1, 2). Similarly, we had postulated that broad-spectrum immunotherapy in growing children might induce remission of asthma earlier or more frequently than would otherwise occur. However, our own study showed no effect on partial or complete remission rates (6). Thus far, therefore, we have been unable to identify unique benefits of immunotherapy that could justify the use of this treatment if it is otherwise not more effective or less toxic than alternatives.

What about patients with moderate to severe persistent asthma who may have uncontrolled symptoms and exacerbations despite multidimensional pharmacotherapy including inhaled steroids? I personally believe that immunotherapy for asthma in the United States is most commonly employed for allergic asthmatic patients with intractable perennial asthma (9, 10). For this reason we targeted perennially allergic children with moderate to severe asthma when we undertook a randomized trial of broad-spectrum injection therapy of 121 children with allergic asthma. About one-half were taking inhaled steroids. Every two weeks medications were adjusted downward by masked physicians using an algorithm. To the surprise of some of us, the results were crisply negative. Immunotherapy had no discernible effect on the requirement for medications, days on oral or inhaled steroids, medical care utilization including urgent care needs, or asthmatic symptoms. Methacholine sensitivity decreased significantly but equally in both groups. Likewise, partial or complete remission from asthma occurred in 31% of the immunotherapy group, but in 28% of the control group. Peak flow rates did improve minimally (mean, 3.8%) in the immunotherapy group. We found trends toward effectiveness for immunotherapy for subsets who were younger at the start of therapy, and those who had milder disease as judged by medication requirements.

My conclusions from these considerations are as follows. I hope they will be your conclusions as well.

1. Immunotherapy may be modestly effective in symptom relief and protection against allergen challenge, but as an adjunct therapy it is not clinically indicated for allergic asthmatic patients with moderate to severe persistent asthma.
2. Immunotherapy for asthma has not been shown to possess unique benefits that are not achievable with alternative remedies.
3. The best clinical results from asthma immunotherapy are seen in younger patients with less established and/or severe disease, but the hypothesis that this targeted population benefits uniquely from immunotherapy has yet to be evaluated.

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References

1. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;151:969-974.
2. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane review). In: The Cochrane library. Issue 3. Oxford: Update Software; 2001.
3. Kemp JP, Cook DA, Incaudo GA, Corren J, Kalberg C, Emmett A, Cox FM, Rickard K. Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. *J Allergy Clin Immunol* 1998;101:188-195.
4. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-1063.
5. Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF Jr, Buncher CR, Busse WW, Bush RK, Gadde J, Li JT, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334:501-506.
6. Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert C, Tonascia, Wheeler B. Perennial asthma in allergic children: a controlled trial of aeroallergen immunotherapy. *N Engl J Med* 1997;336:324-331.
7. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TAE. Survey of fatalities from skin testing and immunotherapy. *J Allergy Clin Immunol* 1993;92:6-15.
8. Committee on Safety of Medicines. Desensitising vaccines. *Br Med J* 1986;293:948.
9. Donahue JG, Greineder DK, Connor-Lacke L, Canning CF, Platt R. Utilization and cost of immunotherapy for allergic asthma and rhinitis. *Ann Allergy Asthma Immunol* 1999;82:339-347.
10. Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. National Institutes of Health Publication number 97-4051. Bethesda, MD: National Institutes of Health; 1997, p 23.

REBUTTAL FROM DR. BOUSQUET

Medicine is an ever-changing science, but "the history of an illness should embody all the facts of medical significance in the life of a patient" (1). This sentence perfectly illustrates the narrow focus of Dr. Adkinson's views on specific immunotherapy (SIT) in asthma. Doctors must not treat patients because they suffer from either nose or chest symptoms but because they have both nose and chest symptoms, which often coexist in asthma (2). Thus, the global approach to the patient is the essence of clinical management. To my great surprise, Dr. Adkinson never discussed the global approach to the allergic patient, which is the major strength of SIT.

In his introduction, Dr. Adkinson wrote that "(SIT) must possess some unique advantages that can't be found elsewhere." He completely forgot my statements: "Besides anti-IgE therapy, SIT is the only current immunomodulatory treatment of allergic asthma" and "SIT is the only treatment that may alter the natural course of allergic diseases." Thus, SIT offers unique advantages and cannot be compared with any other drug that cannot modify the course of the disease, and in particular with relievers such as β_2 -agonists.

The study by Adkinson and coworkers (3) of allergic asthma was extremely well carried out, but the meta-analysis by Abramson and coworkers found that all studies using multiple allergens were negative and that these cannot be used to assess the efficacy of SIT in asthma.

Moreover, Dr. Adkinson's paper is also misleading because he wrote that SIT does not protect against irritants and that there is no consistent effect on nonspecific bronchial hyperresponsiveness. In the Abramson meta-analysis reviewing 12 papers (including reference 3), which studied nonspecific bronchial hyperresponsiveness, the χ^2 Z score is 2.58 in favor of immunotherapy over placebo; I do not know any other controller treatment of asthma that has such an important effect. Moreover, newer studies have confirmed such a positive effect (4, 5).

Thus, Dr. Adkinson's views are probably biased by his own study, which was unfortunately planned a long time ago. He should have more modern views on the global approach to the allergic patient, including the global management of asthma and rhinitis.

References

1. Fauci A, Braunwald E, Isselbacher K, Wilson J, Martin J, Kasper D, Hauser SL, Longo DL, editors. Clinical skills. Introduction to clinical medicine. In: Harrison's principles of internal medicine. 14th edition. New York: McGraw-Hill; 1998.
2. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000;106:201-205.
3. Adkinson N Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert CL, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324-331.
4. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93.
5. Gruber W, Eber E, Miledler P, Modl M, Weinhandl E, Zach MS. Effect of specific immunotherapy with house dust mite extract on the bronchial responsiveness of paediatric asthma patients. *Clin Exp Allergy* 1999;29:176-181.

REBUTTAL FROM DR. ADKINSON

Two of Dr. Bousquet's points require clarification. The first is his claim that immunotherapy improves nonspecific bronchial hyperresponsiveness. The latest update of the Cochrane meta-analysis came to this unfortunate conclusion (1), but those who bother to examine the data will not be convinced. Of 11 studies analyzed, only 2 studies involving 24 treated patients found significant improvement. The largest study, our own trial of 121 children with asthma, did not even trend toward a protective effect. Even if larger or more numerous studies add to the weight of evidence, the magnitude of the protective effect is likely to be tiny relative to the 3- to 4-fold shifts regularly seen with inhaled steroid therapy.

Another noteworthy issue raised by Dr. Bousquet is whether successful results with immunotherapy are restricted to those who are "monosensitized," that is, have a single inhalant allergy. Dr. Bousquet's group has reported that children treated with only *Dermatophagoides* mites developed fewer new allergic sensitivities to other aeroallergens (2). This finding has been confirmed by Pajno and coworkers in Italian children (3). What

this intriguing observation means is not clear. Previous studies have shown that the effect of allergen immunotherapy is immunologically and clinically specific. Do mite extracts contain an adjuvant that can redirect allergic sensitization in general? Why should multiply sensitized patients not benefit from immunotherapy for asthma, as they do for rhinoconjunctivitis? These questions remain unanswered, and as such confound any consensus on the current indications for immunotherapy.

Dr. Bousquet and I agree that the best candidates for immunotherapy are children with mild to moderate asthma, severe perennial allergic rhinitis, and as yet few allergic sensitivities, preferably only dust mite. We participated as a study center in the CAMP study involving 1,041 North American children with mild to moderate asthma (4). Eighty-eight percent of the children had one or more positive skin tests but only 10% were "monosensitized," and of these only 43% were dust mite sensitive. Furthermore, only 12% of this unselected population of children with asthma had perennial rhinitis severe enough to require intranasal steroids year-round. Data from a comparable adult population are not available, but the prevalence of positive skin tests and perennial allergic rhinitis would surely be substantially lower. Thus, applying Dr. Bousquet's criteria, inhalant immunotherapy will be warranted in only a small fraction of patients with asthma and allergies. I rest my case.

References

1. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane review). In: The Cochrane library, Issue 3. Oxford: Update Software; 2001.
2. Des-Roches A, Paradis L, Menardo J-L, Bouges S, Daures J-P, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99:450-453.
3. Pajno G, Barbero G, De-Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mites by specific immunotherapy. *Clin Exp Allergy* 2001;31:1392-1397.
4. Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-1063.