

"ARIA": Global guidelines and new forms of allergen immunotherapy

"Allergic Rhinitis and its Impact on Asthma (ARIA),"¹ which will be published as a supplement to the November issue of this Journal, is the report produced by the second of two international workshops (the outcome of the first was the WHO position paper "Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases," edited by Bousquet, Lockey, and Malling²) that involved physicians specializing in allergy and were completed in collaboration with the World Health Organization (WHO). Both workshops have been endorsed by the American Academy of Allergy, Asthma and Immunology and by numerous other professional organizations throughout the world. Allergic rhinitis was targeted by the WHO because of its impact on asthma, which is becoming increasingly prevalent, particularly in poor communities.

Thirty-four physicians from throughout the world met in Geneva, Switzerland, in December 1999 to begin drafting "ARIA." The document has gone through numerous revisions. An outstanding accomplishment of those involved is that there has been general agreement on the contents of the document by physician representatives who served on the panel. The world is truly becoming global, and uniform standards for evidence-based medicine are being accepted and endorsed.

An aria, according to one of the definitions in Webster's dictionary, is a "striking solo performance,"³ and Jean Bousquet, the chairman of the "ARIA" workshop, is to be congratulated as the major voice in the effort that made the document possible.

"ARIA" begins with a broad classification of rhinitis and suggests that allergic rhinitis—the most common of various forms of the condition—be subdivided into intermittent rhinitis and persistent rhinitis of mild to moderate/severe intensity; this classification is to be used in place of the present classification (seasonal rhinitis and perennial rhinitis).

In the overall scheme of things, allergic rhinitis affects asthma. It usually accompanies asthma or precedes its onset, and asthma cannot be fully controlled unless aller-

gic rhinitis is appropriately treated. Allergic rhinitis also commonly leads to other diseases, such as sinusitis, which also worsens asthma. In summary, IgE-mediated diseases of the upper and lower airways should be perceived as a single entity, and the appropriate treatment of both is necessary for control of allergic respiratory disease.

There are 14 other chapters in "ARIA," among which are chapters on epidemiology and genetics, allergens and trigger factors, management, prevention, and unmet needs for research. Also included is a chapter on recommendations for developing countries; in it, the guidelines are adapted for use in low-income communities. The entire document is a state-of-the-art, evidence-based review of various kinds of rhinitis. It covers all detailed aspects of the disease and makes recommendations for future research. The manuscript has 2776 references.

Of particular interest in "ARIA" is a section on allergen immunotherapy. In the first WHO collaborative project, as described in the "Allergen Immunotherapy" WHO position paper, subcutaneous allergen immunotherapy was recommended for treatment of allergic rhinitis, Hymenoptera hypersensitivity, and allergic asthma. It did not endorse sublingual-swallow immunotherapy, in which the vaccine is held in the mouth for 1 to 2 minutes and then swallowed, or intranasal immunotherapy, in which the allergen is insufflated into the nares. The "Allergen Immunotherapy" position paper, in the section devoted to other forms of immunotherapy, concluded that

Properly controlled, well-designed studies employing sublingual [sublingual should have appeared as *sublingual-swallow*; *-swallow* was inadvertently omitted] and intranasal immunotherapy provide evidence that this form of therapy may be a viable alternative to parenteral injection therapy to treat allergic airway diseases. Further studies are needed to better define the most appropriate patients for this form of therapy, the optimal therapeutic target dose, and its effectiveness as compared to conventional injection immunotherapy.²

The subject of allergen immunotherapy is revisited, though more briefly, in "ARIA"—specifically, in a chapter entitled "Management of allergic rhinitis." Since the publication of the "Allergen Immunotherapy" WHO position paper in 1998, additional controlled studies have been presented in peer-reviewed journals on these forms of immunotherapy. In contrast to the first WHO paper, "ARIA" concludes, in the section on local immunothera-

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py, that high-dose nasal and high-dose sublingual-swallow-specific immunotherapy might be indicated in the following groups:

- some patients with rhinitis, conjunctivitis, and/or asthma caused by pollen and mite allergy
- patients who are not sufficiently controlled by conventional pharmacotherapy
- patients who have systemic reactions associated with injection immunotherapy
- patients who are poorly compliant and refuse injections.¹

In neither document is low-dose sublingual therapy, as currently used by some clinicians, endorsed. Oral immunotherapy, in which the allergen is given in capsule form and swallowed immediately, is also not endorsed in either of the WHO documents.

Seventeen double-blinded, placebo-controlled studies involving the use of high-dose nasal allergen immunotherapy demonstrate that it is an effective form of therapy for allergic rhinitis.¹ Controlled studies showing efficacy have been done with pollens from birch, alder, ragweed, *Parietaria*, and various grasses as well as with house dust mite. The effectiveness is dose-related, and there is a high rate of rhinitis associated with therapy, which might limit its practical use for routine treatment.²

Efficacy of high-dose sublingual-swallow immunotherapy is documented in 13 double-blinded, placebo-controlled studies—primarily for allergic rhinitis, but in some cases for allergic asthma—with regard to vaccines for pollens from birch, *Parietaria*, and various grasses as well as for mite.¹ Two of these studies showed clinical efficacy of sublingual-swallow immunotherapy in double-blinded, placebo-controlled trials through use of multiple standardized grass pollen vaccines.^{4,5} An additional double-blinded, placebo-controlled sublingual-swallow study with a grass vaccine that demonstrated efficacy was published in 2001 and was not referenced in “ARIA”.⁶ At this time, there is only 1 study comparing the 2 forms of immunotherapy. It demonstrates that both sublingual-swallow immunotherapy and subcutaneous immunotherapy are effective, the latter being slightly more efficacious.⁷

Bagnasco et al⁸ studied the kinetics of radiolabeled *Parietaria judaica* major allergen (Par j 1) with sublingual-swallow, oral, and intranasal administration in healthy volunteers.⁸ With oral administration, the radioactive allergen is rapidly detected in the stomach and small intestine with no evidence of radioactivity accumulation at specific sites containing lymphatic tissue. With the sublingual-swallow technique, identical distribution occurs when the allergen is swallowed, but up to 2% of the dose persists sublingually for up to 20 hours, even with extensive mouth-washing. When the intranasal route was used, a relevant fraction of the tracer remained on the nasal mucosa for up to 48 hours and the pattern of plasma radioactivity was similar to those of the oral and sublingual-swallow routes, as was the absorption from the gastrointestinal (GI) tract. Consistent plasma radioactivity increases only after swallowing, leading to the hypothesis that slow absorption and processing of the locally retained allergen occur via the immune system.

The mechanism by which intranasal and sublingual-swallow immunotherapy works is unknown, but this is also the case with subcutaneous allergen immunotherapy. However, it makes sense that dendritic cells derived from the mucosa of the respiratory tract (nasal immunotherapy) or GI tract (sublingual-swallow immunotherapy) could act as allergen-presenting cells, inducing a T_H1 over T_H2 immune response or perhaps even immune tolerance. Studies of sublingual-swallow immunotherapy have demonstrated allergen-specific IgG and IgG4 antibodies.⁹

Both nasal immunotherapy and sublingual-swallow immunotherapy appear to be safer than subcutaneous immunotherapy.^{10,11} However, in 1 sublingual-swallow study in children, urticaria, asthma (some serious), and GI symptoms were noted to be side effects.¹² The most common side effects reported in other sublingual-swallow immunotherapy studies were abdominal pain and/or sublingual itching.¹³

“ARIA” indicates that the efficacious dose for sublingual-swallow immunotherapy necessary to achieve clinical efficacy is at least 100 times greater than that required with subcutaneous immunotherapy. In 2 review editorials on this same subject, Brown and Frew¹³ and Frew and Smith¹⁴ indicated that the optimal dose is 20 to 375 times greater than that required with subcutaneous immunotherapy. Frew and Smith,¹⁴ having thoroughly reviewed the literature on this subject, propose that sublingual-swallow immunotherapy “requires further evaluation before it [can] be recommended for use in routine clinical practice”.

Additional funding and studies are necessary to (1) compare subcutaneous, nasal, and sublingual-swallow immunotherapy with regard to safety and the comparative efficacy of using single allergens and multiple allergens derived from different animal and botanical sources and (2) explore the mechanisms that result in clinical improvement for each form of therapy. Another issue is safety. Asthma has been associated with sublingual-swallow immunotherapy, but fatalities have occurred with subcutaneous immunotherapy; if the 2 forms of therapy are equally efficacious, safety alone might make sublingual-swallow immunotherapy the preferable form of treatment. Yet another issue is the cost-effectiveness of one form of therapy versus that of another. The cost of allergen vaccine will be considerably higher with high-dose sublingual-swallow immunotherapy; however, such therapy is administered at home, and there is a resultant decrease in the overall cost. A current meta-analysis of both nasal immunotherapy and sublingual-swallow immunotherapy would also be useful.

Like the “Allergen Immunotherapy” WHO position paper,¹ “ARIA” indicates that the responsibility for standards of care are allocated to physicians in individual countries. Before governments or private health care plans in North America are willing to reimburse for high-dose intranasal or high-dose sublingual-swallow immunotherapy, position papers supporting such therapy to treat allergic diseases will have to be produced by national professional organizations, such as the American Academy of Allergy, Asthma and Immunology. The

Joint Task Force on Practice Parameters, which represents the major allergy organizations, has established guidelines for subcutaneous allergen immunotherapy and should do so for any other form of immunotherapy endorsed by its parent organizations. Such guidelines would include recommendations pertaining to dosing, intervals between doses, therapy administration, acceptable formulas by which to assure vaccine stability, methods of documenting treatment, and other details necessary for effective allergen immunotherapy.

Other forms of immunotherapy for IgE-mediated diseases are on the horizon. Anti-IgE (omalizumab) is in clinical trials, and other biologic targets for pharmacologic intervention have been identified and are under investigation. For the time being, subcutaneous allergen immunotherapy remains the standard of care for allergen immunotherapy in most parts of the world. However, newer and perhaps more efficacious forms of immunotherapy are under investigation, and they might in time supplement or replace it.

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