



Modern approaches to therapeutic vaccination as treatment for Type 1 respiratory hypersensitivity (allergy) treatment

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The incidence of respiratory and other allergies has increased dramatically in many countries over the last few decades. Drug treatment is symptomatic and has a minimal effect on the underlying immunological dysfunction. This disease process may, however, be modified by allergy vaccination, which is typically applied by injecting increasing strengths of the offending allergens. Its use has been fairly limited owing to long injection schedules involving many visits to the physician, occasional local or systemic side effects, perceived limited efficacy and poor compliance. A greater understanding of the immunological mechanisms involved in allergy vaccination has led recently to the development of new generations of products with properties that address some of these issues, and these advances are likely to increase the successful use of the therapy.

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Type 1 hypersensitivity is characterized by high levels of allergen-specific immunoglobulin (Ig)E antibody, which fixes to mast cells and initiates the release of histamine and other mediators on recontact with allergen from sources, such as pollens (from mainly entomophilous plants), mites and their feces, animal danders, molds and some foods. Symptoms can occur in various organs, but typical respiratory allergy is associated with rhinoconjunctivitis and/or asthma. Some hours later, a second, late-phase reaction occurs, which is associated with inflammation and cell infiltration. An excess of T-helper cell (Th)2 lymphocyte and inappropriate Tregulatory cell activities are thought to be responsible for the immunological dysfunction [1].

It is well accepted that the incidence of allergy has increased, particularly in the developed world. A number of suggestions have been made to account for this increase:

- The hygiene hypothesis [2,3] suggests that a modern, cleaner lifestyle that avoids the contact of very young children with oral–fetal bacteria, such as those found in farming

environments, leads to delayed or poor development of Tregulatory cells and a more pronounced Th2 response, which is currently believed to lead to sustained IgE responses. Overuse of antibiotics has also probably contributed to this effect [4]

- Certain types of pollutants, such as ozone and diesel particles, have been demonstrated to be adjuvants for IgE production in experimental animals [5], as well as probably being carriers of pollen grains
- Pollutants have also been demonstrated to promote the release of certain pathogenesis-related proteins (PRPs), some of which are allergens, from the pollen of some plants [6]

Various forms of therapy are used to treat the symptoms of the disease, such as antihistamines, bronchodilators, local corticosteroids and leucotriene antagonists. Although in some patients such treatment is very beneficial, complete relief from symptoms is not necessarily achieved and the disease may continue to worsen under the cover of the drugs, with rhinoconjunctivitis progressing to

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asthma (the 'allergic' or 'atopic march') [7]. Humanized monoclonal anti-IgE antibody is also in use in some countries to treat patients, especially in cases of life-threatening allergic asthma and multisensitization [8]. It is still not yet clear whether this novel product prevents symptom occurrence induced by IgE or if it has, in addition, some propensity to divert the immune response away from the Th2 phenotype.

Allergy vaccination, previously termed hyposensitization or allergen-specific immunotherapy, can change the course of the disease, blunt the 'allergic march' and, after several years' treatment, a semipermanent cure can often occur, and thus, it has advantages over symptomatic treatment [9]. The treatment has been limited until now to specialists' surgeries owing to the long injection schedules used, the fear of generalised, but rare allergic reactions and the need for very precise diagnosis to enable the specific allergy vaccine to be prescribed.

Allergy vaccination has been demonstrated to lead to the induction of IgG antibody, particularly of the IgG₄ subclass, which some allergists believe to be at least partly responsible for the benefits of the treatment, as it may prevent allergen from being taken up by IgE bound to FcεR2 on antigen-presenting cells (APCs) and boosting an IgE response [10]. Alternative roles for IgG₄ antibody have been suggested. Mast cells and basophils have been demonstrated to have surface receptors for IgG₄. It has been conjectured that reaction of allergen with this cell-bound antibody might inhibit its reaction with IgE, and thus inhibit the release of anaphylactic mediators [11,12]. A change from a more pronounced allergen-specific Th2-like response to a more pronounced Th1-like response has been observed based on the changes in cytokines released in *in vitro* cell studies [13]. This leads to an eventual downregulation of specific IgE due to reduced interleukin (IL)-4, -5 and -13 from T cells and a reduced late-phase response due to reduced IL-5 levels. More recently, increases in Tregulatory cell activity, often of the CD4⁺25⁺ phenotype, have been observed [14]. The cytokines IL-10 and transforming growth factor (TGF)-β can especially reduce the allergen-specific T-cell response of, in particular, those T cells releasing Th2 cytokines. IL-10 and TGF-β can promote increases in non-inflammatory blocking antibodies of the IgG₄ and IgA₂ isotypes, respectively. Studies of the mechanisms underlying the type of immune response initiated by an antigen have demonstrated that the inter-relationship between the more primitive innate and acquired immune responses is of key importance. Different Toll-like receptors (TLRs) on APCs respond to molecular patterns associated with the antigen challenge and direct the T-cell response and the help to B cells via the release of mediators, such as IL-12, IL-10, TGF-β and others [15,16]. Thus, some modern formulations already in clinical use, and others in development, can be designed with clearly defined targets.

Optimal therapy

Although allergy vaccines have been used for approximately 100 years, the general principles of their use have not changed. During a course of rising-strength injections, each

desensitizes progressively so that the next injection is tolerated up to a maximum tolerated dose for each patient or, in the case of more standard products, to a dose that is optimal in most patients, as indicated by placebo-controlled clinical studies. However, the issues of safety, efficacy, convenience, cost, convenience and compliance are all factors that have led to different approaches.

Allergy vaccination is effective in the first year of treatment in some patients with certain vaccine preparations and, if continued for 3–5 years, a long-lived improvement is often found, without the further need of therapy [17]. The treatment may not be effective in all patients, but in many cases, symptomatic therapy is only required at times of unusually high allergen exposure. It is not clear why all patients do not respond positively, but incorrect diagnosis and sensitivity to unknown allergens can both be responsible.

Guidelines for the use of allergy vaccination vary on a national basis, even though there is a WHO position paper on the subject, but all specify that subcutaneous injection therapy should be administered only by those trained in its use [18]. Many different formulations, allergen forms and adjuvants have been used over the years. Sometimes, these are made on an individual patient basis, and are often mixtures made according to an individual's sensitivity, which is used by clinicians on a named patient basis. In Europe, these are made in factory facilities that should be cleared by national licensing agencies for the manufacture of 'specials', whereas, in the USA, the formulations are often prepared by the physician. Other standard licensed allergy vaccines are also available in some countries.

Traditionally, long schedules of aqueous formulations of allergen extracts have been used, typically employing at least 20 injections per year, and often lacking good patient compliance. A long and cautious up-dosing schedule is necessary to ensure good safety and, in spite of this, severe adverse reactions are still reported occasionally. However, in most countries, particularly in Europe, the need for this large number of injections has been alleviated by the addition of depot adjuvants, such as aluminium hydroxide [19]. More recent and more easily degradable depot adjuvants for injection courses are the poorly soluble amino acid L-tyrosine and calcium phosphate, which are currently used in many vaccines [19]. Chemically modified allergens (often termed allergoids) were introduced some years ago to increase the safety of the vaccines by reducing their immediate reactivity with IgE antibody [20], and thus allow a further reduction of the number of injections required [21]. Such products, using allergens chemically modified by a variety of reagents, are used widely in Europe and have contributed towards the safer use of allergy vaccination.

The finding that sublingually administered (sublingual immunotherapy [SLIT]) allergy vaccines have some level of efficacy while producing only minimal adverse events has 'changed the face' of allergy vaccination in some countries and has recently been confirmed by an exhaustive meta-analysis [22]. SLIT is administered at home, which should increase convenience and compliance and enhance the pharmacoeconomic advantages of

allergy vaccination. There is some debate over whether compliance is satisfactory, but as yet, there has been no thorough investigation of this issue. Unfortunately, SLIT is generally thought to be less efficacious than subcutaneous therapy, and will probably require more optimized dosing; the addition of a mucosal adjuvant or a novel formulation may help to achieve its full potential.

The mechanisms involved in a successful vaccination are becoming clearer, thus providing targets for new formulations. Although views on these mechanisms are changing rapidly, we appear to be moving toward a consensus, as described previously. There are several experimental allergy vaccines that have been designed with defined targets. In particular, various T-cell reactive peptides [23] and recombinant allergen-based molecules with very low reactivity with IgE are showing some promise [24]. Also, a conjugate of a major allergen Amb a 1 from ragweed pollen and an immunostimulatory sequence of DNA (ISS) containing a CpG motif is well advanced in clinical trials. The CpG DNA is an agonist for TLR-9 on APCs and is probably responsible for the release of IL-12 and the stimulation of a cytokine profile more consistent with a Th1-cell response that, for soluble antigens, such as allergens, leads to a switch away from allergen-specific IgE to G subclass antibodies [25]. This exciting approach has been taken further by the use of another TLR agonist, detoxified monophosphoryl lipid A (MPL[®]), which is extracted from the cell wall of *Salmonella minnesota* [26]. This agonist is injected as an immunomodulator combined with allergoids as a depot form with L-tyrosine. The addition of MPL has allowed a reduction in the number of injections required, from several to only four per course, to achieve efficacy [27]. TLR4 and to some extent TLR2 on APCs are involved as targets for MPL [28]. Allergoid/MPL/tyrosine vaccine formulations have been recently introduced for clinical use. Recombinant allergens are currently being studied in clinical trials. A mixture of recombinant molecules is being used in some cases, presumably necessary for addressing allergy to a variety of individual allergen molecules that are present in a source material, such as grass pollen [29,30]. Although there is no *a priori* reason why such a strategy should prove more effective or safer than using native extracts, a claim of improved quality and reproducibility of manufacture could be made. In addition, one might avoid the potential, but not proven, disadvantage of the injection of non-allergen molecules present in a source material. A more exciting possibility is presented by the use of mutant proteins derived from recombinant allergens that have their IgE-combining sites altered by genetic manipulations such that they do not react with IgE antibody [31]. These molecules should potentially be safer to use than conventional allergens, but there seems no obvious reason why they should be more effective.

These approaches have the capacity to revolutionize allergy vaccination and to make it a more widely acceptable choice of treatment. In addition to increased efficacy and enhanced safety of these innovations compared with older products and improved compliance, a pharmacoeconomic study has already demonstrated the advantages of even some older products over symptomatic therapy [32]. The pharmacoeconomic

advantages would be strengthened by immunotherapy employing further reductions in the number of injections (e.g., four are now possible) or the sublingual route.

Factors affecting choice of therapy

One factor that has limited allergy vaccination has been the safety of the procedure, which has been discussed in the WHO position paper [18]. Clearly, injecting solutions of proteins to which patients are hypersensitive may result in, at the least, a large local reaction and, at worse, a life-threatening event. Thus, formulations and strategies are often chosen that reduce the likelihood of these adverse events occurring. Allergoids are often used, as described previously, to reduce the reactivity of the vaccine with mast cell-bound IgE antibody, as shown by skin-testing [33]. Depot forms make the allergens or allergoids less immediately bioavailable; stepwise-injection regimens are designed to decrease the likelihood of reactions and adjuvants are used to enhance the immune response, which allow a reduction in the concentration of the allergens or allergoids required for satisfactory efficacy [19]. Other strategies being studied rely on the T-cell reactivity of allergen-derived peptides that have a very much reduced reactivity with IgE, although none of these have been advanced to clinical use [23]. Protein engineering may reduce or eliminate IgE-binding sites, which also shows some promise, but resulting vaccines are not available as yet [30,31]. The very complex vaccine formulations used nowadays have high batch-to-batch reproducibility owing to advances in immunoassay (e.g., enzyme-linked immunosorbent assay [ELISA] inhibition), which significantly reduces the risk of a rogue batch causing serious side effects. Despite these increases in the safety profile of the treatment, allergy vaccination should still only be administered by clinicians well trained in its use. Some allergists carry out the treatment under the cover of antihistamines, but others believe that this could be an issue, as a rescue treatment modality could be lost if the patient were to have an adverse event. If sublingual treatment can be made more effective, its excellent safety profile compared with injected products should extend the application of allergy vaccines.

Allergy vaccination is used in most cases to treat only well diagnosed IgE-based respiratory allergy when the disease is associated with a relatively few known causative allergens. Food allergies (e.g., peanut) are essentially not addressed. Although the treatment has been used successfully to treat asthma, its use is often restricted to those patients suffering from rhinitis, conjunctivitis and mild asthma.

As described earlier, guidelines for the use of allergy vaccines are available on a national basis in some countries, as well as on an international basis, and should be taken into account when allergy vaccination is planned [18]. These describe in detail how the products should be used and, to some extent, also highlight some national differences. In the UK, fewer allergy clinics compared with many other European countries has resulted in relatively fewer allergy vaccines administered. UK guidelines provide a waiting time of 1 h in the surgery after injection compared with 0.5 h in Europe.

Injected products in the rest of Europe are often given with adjuvants or are allergoids, and are prepared in audited factories as final products, often on a batch basis or for individual patients. In the USA, the practice is often for allergologists to obtain extracts from audited suppliers and to tailor personally the products for each patient, frequently mixing a large number of over ten allergens, whereas Europe complies with a more cautious approach for combinations [18].

Expert commentary & future perspective

Allergy vaccination is currently used in only a small proportion of allergic patients for reasons described previously; yet the treatment can correct, permanently in some people, the underlying disease mechanisms and, in this respect, is superior to symptomatic therapy. Also, in these patients it can eventually be superior in terms of pharmacoeconomics. The specificity of the vaccination is clearly a limitation that it is difficult to overcome. In fact, some strategies being developed, such as the use of single recombinant allergens, can exacerbate this situation. Some of the modern formulations now being used contain allergens with reduced IgE reactivity, new depot forms and adjuvants designed to downregulate the Th2-type allergic response and induce allergen-specific Tregulatory cells. These formulations, with an enhanced safety profile and reduced number of injections, should encourage the wider use of vaccination. Thus, particularly in the USA, the use of very long aqueous injection courses could enter into decline. The safety profile of sublingual allergy vaccination is to such a high standard that the products can be self-administered at home by the patient. Although a number of formulation changes have been introduced, such as fast-dissolving tablets, to increase compliance, these are unlikely to enhance significantly the efficacy of the more traditional aqueous sublingual formulations. It is generally agreed that sublingual allergy vaccination is probably less effective than subcutaneous injection therapy. A 'step change' in efficacy is

needed, which may perhaps be provided by designing a more optimal dosing regime and, eventually, by some form of mucosal adjuvant. Such a change is likely to increase the usage of allergy vaccination considerably.

If the hygiene hypothesis of allergy is correct and ways of identifying those children who are most likely to become allergic are strengthened, then use of some of the modern adjuvants, such as MPL together with a mixture of common allergens, in children, before the development of their allergic symptoms, may revolutionize the treatment of this condition. The current therapeutic vaccination strategies may then be supplemented by the use of prophylactic vaccines for allergy.

Key issues

- It will be important to find a way to increase the efficacy of sublingual allergy vaccination.
- Various Toll-like receptor agonists (to act as immunomodulators as components of allergy vaccines) need further evaluation to enhance efficacy and to reduce the number of injections required.
- Recombinant allergens and muteins should be developed into efficacious vaccines.
- Immunotherapy for food allergies, such as peanut allergy, should receive more attention
- The safety issues regarding immunotherapy must be addressed (e.g., by reducing aqueous immunizations), which will encourage the therapy to become more mainstream.
- Prophylactic vaccination should be studied.
- If these improvements are realized, it will be necessary to have a simpler licencing system that would allow a cheaper and faster approach to treat the large array of allergic sensitivities that are diagnosed.

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