

Allergy Vaccination Receives a Positive Reaction



Allergic rhinitis constitutes one of the world's single largest pharmaceutical markets. Going back 100 years to examine the biological processes of this common disease, a new vaccine is poised to reinvent its treatment, says consultant Kevin Wilkinson

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As one of the world's most common diseases and responsible for countless hours lost productivity and school time, allergic rhinitis (AR) – commonly known as hay fever – affects almost one-third of North American and European populations. Treatment options for this condition were first developed almost 100 years ago and now gross more than \$4 billion annually. Here we examine the basic mechanisms and pathology of AR, and take a glimpse at a new vaccine that could redefine what we call 'conventional' for treatment of this frustrating condition.

ALLERGY VACCINES

Allergic rhinitis (AR) is an overreaction of the immune system to otherwise innocuous airborne antigens, such as pollen, mould or dust mites. All allergic reactions are hyperactive immune responses arising from pre-existing antibodies and, although there are a number of classifications of allergy, the most common is known as a type I hypersensitivity reaction. In this case, inhaled allergens crossing through the mucosal membranes in the nose and throat cross-link with preformed IgE antibodies bound to high-affinity FcεRI receptors on the surface of mast cells.

Mast cells themselves are found in connective tissues throughout the body and usually serve to alert the immune system to local infection. In the case of allergy, however, they have the unwanted ability to provoke an allergic reaction in response to allergens that aren't associated with an invading pathogen. Upon binding of the allergen to the surface IgE, mast cells become activated and within seconds they release preformed stored mediators via granule exocytosis. Responsible for the immediate responses of an allergic reaction, these mediators include histamine, which elicits vasodilation, bronchoconstriction, smooth muscle activation and itching, and TNF-α, which causes the upregulation and recruitment of leukocytes and lymphocytes (1).

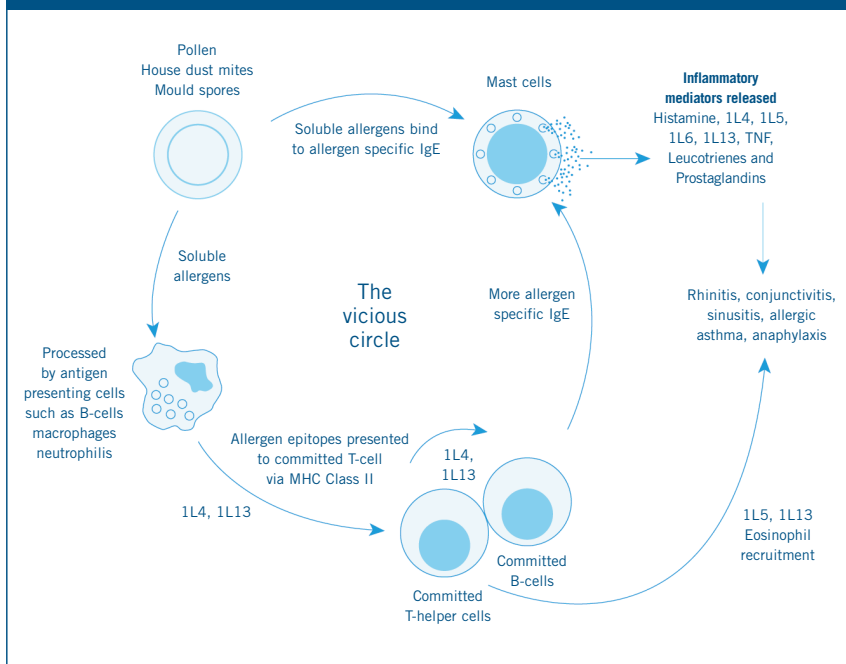
Activation of the mast cells also leads to their synthesising of leukotrienes and cytokines. These effector molecules act downstream in the allergic late-phase response, recruiting T_H2 lymphocytes, eosinophils and basophils – all of which express the FcεRI receptor. These cells can then sustain and prolong early-stage symptoms, while further contributing to the immunopathology of AR.

THE AR POPULATION

Estimates for the total number of people affected by AR vary considerably depending on the geographical location and socio-economic conditions of the population being examined. Although there are several different reasons for this, it is generally believed that hereditary and environmental contributions, as well as differences in local plant populations, play the largest roles in determining incidence and trigger allergens. In developed nations such as the US and UK, for example, AR is estimated to affect 30 per cent of adults and up to 40 per cent of children (2,3).

Approximately 20 per cent of patients with AR also have asthma. Children are particularly vulnerable and many with AR frequently go on to develop asthma later in life. In such cases, it is thought that the patient's upper and lower airways may be affected by inflammatory processes common

Figure 1: The vicious circle



Allergic Rhinitis (SAR) and those with Perennial Allergic Rhinitis (PAR). SAR is associated with outdoor allergens including grass, tree and weed pollens. These affect the nose and eyes of susceptible individuals and, less frequently, the lungs. Symptoms of SAR include sneezing, rhinorrhoea and irritation of the eyes. In contrast, PAR is associated with indoor allergens, particularly dust mites and animal allergies. Although PAR symptoms may be prevented by minimising contact with the causal allergens, the prevalence of pollen at certain times of the year makes avoidance for SAR sufferers nearly impossible. Some allergic patients suffer from both SAR and PAR, which has a highly adverse impact on their quality of life.

Today, symptomatic treatment of SAR represents one of the single largest pharmaceutical markets worldwide, with

to both conditions, linking the two diseases. This is commonly referred to as the 'allergic march' and requires early disease modifying intervention beyond that available through simple symptomatic treatment. Unfortunately, asthma is not the only condition associated with AR, as patients with a history of dermatitis, eczema and other atopic diseases are at increased risk of its development.

One of the more concerning issues in the epidemiology of AR, however, is its rising incidence worldwide. Again, the causes of this are believed to be multifactorial with a few sources thought to be more prevalent. One of the most important of these is known as the 'hygiene hypothesis'. In the clean environments of modern industrialised nations, children are no longer exposed to a wide variety of microbes and illnesses that help to naturally develop the immune system. A lack of microbial exposure may therefore lead to an understimulated immune system and one consequence is the generation of IgE antibodies causing hypersensitivity to allergens. Mast cells, which might normally have developed to fight parasitic worms or bacterial infection, instead become activated by common environmental antigens such as pollen grains. Although this process has yet to be proven, many studies have shown a correlation between an increase in affluent lifestyle and the development of asthma and AR.

Among other possible causes that are being investigated for the rise in AR is the increased exposure to environmental toxins in developed nations. Air quality in population-dense cities is often very poor and the presence of toxic materials introduces new potential allergens. Environmental toxins are, however, more commonly associated with vasomotor rhinitis, a non-allergic form of the condition.

In terms of trigger allergens, persons affected by AR can be broadly segmented into two groups, those with Seasonal

total sales in 2004 of \$4.3 billion. These treatments include the use of antihistamines and both steroidal and non-steroidal sprays. These drugs relieve symptoms, but need to be taken on a daily basis throughout the pollen season in order to be effective. Missing a dose of symptomatic treatment may quickly lead to a recurrence of symptoms. In some cases, patients may also develop a tolerance for their medications, reducing their effectiveness.

100 YEARS OF TREATMENT

Studies with allergy vaccines were first conducted by Noon and Freeman at St Mary's Hospital in London. Published in the *Lancet* in 1911, their groundbreaking article outlined the successful treatment of SAR using subcutaneous inoculation of pollen extract using a sequence of increasing doses. Hypersensitivity of the allergic patient is corrected by allergy vaccination (also known as allergy immunotherapy and desensitisation), which, like all other vaccines, works by reinforcing the body's own defence mechanisms. Although the precise details have yet to be elucidated, allergy vaccines are believed to function by increasing the activity of T_H1 cells and/or reducing the activity of overstimulated T_H2 cells. Regardless, vaccines are the only form of SAR treatment available that are essentially curative, modifying the underlying mechanism of immune action against the allergen, rather than providing symptomatic relief. Further to a significant decrease or elimination of symptoms, allergy immunotherapy can also halt the allergic march and prevent the later development of AR-related asthma.

As with other medical and pharmaceutical markets however, the history and scientific approach to AR vaccine development has progressed differently between the US and Europe. In the US, manufacturers have been involved only in the provision of bulk allergen extracts to physicians. Physicians have then traditionally

taken these bulk extracts and prepared them for injection using their own experience as a guide to determine suitable dosing schedules. As the physician is involved in the vaccine manufacturing and preparation process, the Food and Drug Administration is not involved in its usual oversight function.

Naturally, the use and safety of the manufactured bulk products at such high doses is uncertain. Physicians have, therefore, developed lengthy low-dosing schedules in order to maintain safety and deliver sufficient total doses. These regimes often involve 30-40 (and occasionally more) injections over the span of a year, which is then repeated in two follow-on years at lower frequency. In total, patients may then receive 50-100 injections in order to complete a treatment course. According to the American Academy of Allergy and Immunology, over 33 million AR vaccine doses are delivered to patients in the US each year, making this by far the world's largest pharmaceutical market. Estimated sales of bulk materials to physicians in 2005 approached \$100 million.

In contrast, European manufacturers generally provide physicians with AR vaccines ready for injection. Manufacturers have developed techniques involving modification of the allergen extract and the use of adjuvants to improve the safety, efficacy and convenience of these products. The result has been an up to tenfold reduction in the number of doses required to have effect and a significant reduction in the number of systemic side effects. Patient acceptance and compliance levels have consequently improved as well. In 2005, total sales of allergy vaccines in Europe approached €250 million; the German market occupies the largest portion of this at a value of over €110 million.

RAISING THE BAR OF AR TREATMENT

One of the most innovative developments to recently enter the AR treatment market is based on a novel adjuvant, MPL[®], a detoxified derivative of lipid A, obtained from *Salmonella minnesota*. The incorporation of this adjuvant in vaccine formulations provides a number of benefits. Released in Germany in 1999, Pollinex[®] Quattro (manufactured by Allergy Therapeutics) provides an immunological skew towards a T_H1-

like response, which may counteract the T_H2-like response (associated with the generation of IgE antibodies). The addition of the MPL adjuvant provides for improved efficacy compared with contemporary vaccines and permits shorter treatment periods. Studies of this 'ultra-short course' AR vaccine demonstrate that an effective dose can be delivered in four injections over three weeks (4).

The vaccine uses allergens that have been chemically modified (allergoids) employing glutaraldehyde to cross-link the proteins. The use of allergoids in allergen-specific immunotherapy has existed for several years and their primary function is to maintain the immunogenicity of the therapeutic allergen, while minimising IgE binding activity. In the vaccine, modified allergoids are absorbed onto a depot adjuvant, L-tyrosine, which allows for slower absorption by the patient and improved safety. It is thought that MPL also acts synergistically with the L-tyrosine in the induction of the T_H1 immune response.

The global introduction of a vaccine that is easy to administer is likely to cause a sizeable shift in the treatment and management of AR. Currently, symptomatic treatments constitute the vast majority of segment sales, largely due to their relatively low cost, wide availability and the simple fact that they don't rely on a three-year injection programme. Although the scale is impossible to predict, the availability of a cost-viable vaccine that could be delivered in a few trips to a local allergy specialist is certain to be attractive to a large portion of AR sufferers – especially when allergy season starts again. ♦

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References

1. Janeway CA and Travers P, Ed. *Immunobiology: the immune system in health and disease* – Third edition, Garland Publishing, New York, 1997
2. Dykewicz MS *et al*, Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology, *Ann Allergy Asthma Immunol* 81: pp478-518, 1998
3. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC, *Lancet* 351: pp1,225-1,232, 1998
4. Drachenberg KJ *et al*, A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections, *Allergy* 56: pp498-505, 2001

Figure 2: Allergy vaccine patients

