

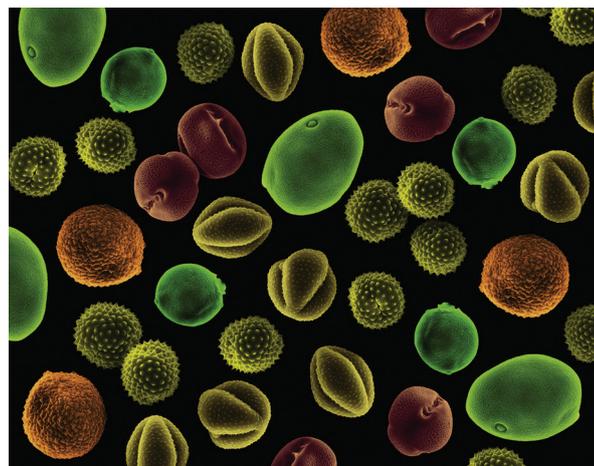
Allergen immunotherapy for respiratory allergic disease in Australia in 2016

Choosing personalised immunotherapy is a complex decision

Australia has one of the world's highest rates of asthma and allergic rhinitis — up to 20%¹ and 30%² respectively — leading to a considerable burden in terms of reduction in quality of life, functional impairment and mortality; there were 419 deaths due to asthma in 2014.³ These conditions can be caused or triggered by exposure to aeroallergens in susceptible individuals. “Epidemics” of severe and even fatal asthma after springtime thunderstorms, as seen in Melbourne in November 2016 (<http://www.abc.net.au/news/2016-11-29/thunderstorm-asthma-eighth-person-dies-from-melbourne/8074776>), are triggered by allergenic pollen microparticles, which (unlike intact pollen grains) penetrate into the lower airways. It is therefore important to understand the patterns of allergic sensitisation and allergen exposure of patients, which can vary geographically as recently demonstrated.⁴ This understanding informs advice regarding allergen avoidance strategies (where possible), the introduction of controlling medications to counteract allergen exposure, and the use and selection of allergen immunotherapy.

Respiratory allergic disease can be effectively treated with allergen immunotherapy, in which allergic reactivity is reduced by long term (3 years) regular repeated exposure to the relevant allergen. This exposure may occur via injection as subcutaneous immunotherapy (SCIT) or by the transmucosal route in sublingual immunotherapy (SLIT), resulting in a reduction in rhinitis and asthma symptoms and medication requirement. Unlike pharmacotherapy, immunotherapy may actively alter the course of allergic diseases, including prevention of asthma in children who are treated for rhinitis,⁵ reduction in the development of new allergic sensitisations,⁶ and prolonged benefit after completion.^{7,8} Allergen immunotherapy has remained fundamentally unchanged since it was first reported in 1911,⁹ but has been underpinned in recent years by an extensive evidence base with multiple clinical trials and meta-analyses.¹⁰

The benefits of allergen immunotherapy may be compared with standard care with medications, such as antihistamines and intranasal corticosteroids for allergic rhinitis, and inhaled corticosteroids and bronchodilators for asthma. However, there are few direct comparisons, and many trials have involved patients who were inadequately controlled by standard medication and have included rescue medications in the control arm. Two randomised open trials in asthma directly compared inhaled budesonide with SCIT¹¹ and SLIT.¹² The results of these trials showed that while budesonide resulted in more rapid improvement in symptoms and in the forced expiratory volume in 1 second,¹¹ immunotherapy was associated with a greater magnitude of symptom reduction in the upper and lower airways, a greater improvement



Scanning electron microscope image of allergenic pollen (false colours)

in methacholine sensitivity,¹² and improvement that persisted after cessation of treatment.¹¹ A pooled analysis of separate rhinitis trials has indicated that symptom improvement with SLIT is superior to oral antihistamines and similar to intranasal corticosteroids.¹³

Allergen immunotherapy is specific (ie, it does not reduce immune reactivity to unrelated allergens) and its efficacy depends on the identification of pathogenic allergic triggers, which requires two criteria: the patient's allergic sensitisation pattern and allergen exposure. Another factor to be taken into account is the degree to which the condition is caused, driven or triggered by allergy compared with non-allergic factors, such as irritant sensitivity, infection and chronic inflammation. A careful history, detailed allergy testing, and knowledge of geographical variation in exposure are crucial to correctly identify the relevant allergens.

Insofar as allergic triggers vary with each patient and therapy can be individualised, allergen immunotherapy represents personalised medicine. Indeed, detailed studies have revealed layers of complexity. Allergens comprise mixtures of allergenic protein components. At least 20 allergenic proteins have been identified in house dust mites, of which several are dominant.¹⁴ Patients show variable patterns of immunoglobulin E (IgE) reactivity within this mixture. Pollens also comprise many allergenic proteins, some of which are cross-reactive between species, while others are unique. Each person is sensitised to a different combination of allergens, although there are common patterns that may vary geographically.⁴ Component testing, which identifies specific IgE to individual allergenic proteins or epitopes, promises to provide further information to guide the choice of allergens for immunotherapy.¹⁵

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The complexity of allergen extracts, their derivation from natural sources, and the large and diverse range of allergens do not fit well into the pharmaceutical product regulatory framework. Recent manufacturing efforts have focused on large-scale production of single common allergen therapeutic products, which facilitates standardisation, quality control, commercial cost effectiveness and registration, but is inimical to personalised therapy. Some of the more common pollen and house dust mite injection extracts have now been registered with the Therapeutic Goods Administration, as have grass pollen and dust mite immunotherapy tablets. However, many diagnostic and therapeutic products remain unregistered and are obtained under the authorised prescriber system or are supplied on a named patient basis, which may limit access to practitioners and patients.

Problems with injection immunotherapy include the risk of acute reactions (anaphylaxis) and prolonged weekly uposing protocols. One method of dealing with these problems is the development of modified allergens (allergoids) with reduced IgE reactivity, and hence improved safety and shorter uposing periods. These preparations appear to be effective, but evidence is limited.

The major development in allergen immunotherapy over the past 20 years has been the re-emergence of SLIT. High doses are required to produce a therapeutic effect, which results in a higher cost. SLIT may be delivered as drops or dissolvable tablets. Tablets deliver a consistent high concentration of allergen, but they cannot be formulated to individual (personalised) allergen requirements. Fixed formula tablets are most applicable for house dust mite immunotherapy, and recent studies have demonstrated a marked rhinitis symptom reduction after deliberate allergen exposure in a challenge chamber,¹⁶ and a clinically significant reduction in time to asthma exacerbation after the withdrawal of inhaled corticosteroids,¹⁷ which suggests the tablets' potential as add-on therapy in house dust mite allergic asthma.

Pollen tablet SLIT has been shown to be efficacious in seasonal allergic rhinitis in northern hemisphere settings, although the degree of symptomatic benefit has been questioned.¹⁸ The pollen SLIT tablets currently available are formulated only with temperate grass species (eg, ryegrass and timothy) and do not cover the subtropical grasses (eg, Bahia, Johnson and Bermuda) commonly found throughout Australia.¹⁹ It has been shown that patients in northern Australia may be primarily sensitised to subtropical grass pollens, with limited cross-reactivity to temperate grasses.²⁰ There is no empirical evidence that immunotherapy with temperate grass pollen extracts will optimally treat those with primary or concurrent subtropical grass pollen sensitisation.

Numerous trials have now established the efficacy of SLIT, although it has been difficult to determine its

relative efficacy compared with SCIT due to the paucity of direct comparative trials. Detailed review of multiple trials has led to a conclusion of equipoise, whereby an apparent efficacy advantage of SCIT is counterbalanced by the safety and tolerability advantage of SLIT.¹⁰ However, concerns such as cost to patients and to private and public health systems, suitability of products for individual patient allergen profiles, and compliance must also be considered. Optimal long term benefits are attained by the completion of a recommended 3-year treatment, but in practice (as opposed to clinical trials) adherence is often poor. Completion rates have been reported to be as low as 23% for SCIT and 7% for SLIT.²¹ In children, the rate of discontinuation of SLIT was 46% by 6 months, attributed to poor tolerance or ineffectiveness.²² Regular patient monitoring may be the most important tool in maintaining adherence, with recent focus on the use of various forms of information and communication technologies.²³

Clinical observation reveals that some patients benefit more from immunotherapy than others, yet most clinical trials show only aggregate results and do not indicate response rates. A major disappointment of recent large-scale trials has been the lack of investigation on the determinants of individual response and the failure to provide markers to predict those who are most likely to benefit from immunotherapy. Immunological changes resulting from immunotherapy are investigated, but often they are not correlated with the degree of clinical benefit. The duration of improvement has been demonstrated in various trials for 2, 5 and even 10 years after completion of therapy, yet many patients relapse after variable periods, and there are currently no markers to predict this.

Allergen immunotherapy by the subcutaneous or sublingual route is an important modality in the management of allergic respiratory disease. It has the potential to abrogate allergic rhinitis and to reduce allergic triggers of asthma exacerbation. The choice of personalised immunotherapy with SLIT or SCIT is a complex decision, which depends on the availability of optimal allergen products selected according to patient sensitisation, exposure and preference. High-dose allergen tablet immunotherapy may provide an important new option in the management of house dust mite allergy, whereas for most individuals with pollen allergy, SLIT products more suited to local allergens are likely to be required, and clinical studies in Australia are necessary before their adoption.

Competing interests: William Smith has consulted for Stallergenes and Seqirus. Frank Kette has consulted for Seqirus.

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