Making Education Easy

April 2013

This is a review of a presentation by Professor Ulrich Wahn on recent allergy and immunotherapy research. The evening provided up-to-date information on prevalence and progression of atopic disease and the available treatment strategies. The event was attended by clinicians specialising in allergy medicine and was sponsored by Stallergenes (Australia).

In this review:

Abbreviations used in this review

AD = atopic dermatitis
AIT = allergy immunotherapy tablet
AUC = area under curve
CI = confidence interval
EMA = European Medicines Agency
IgE = immunoglobulin E
IR = index of reactivity
MoE = magnitude of efficacy
Phl p = *Phleum pratense*
PIP = Paediatric Investigatory Plan
RC = rhinoconjunctivitis
RCT = randomised controlled trial
RTSS = rhinoconjunctivitis total symptom score
SARg = grass pollen-related seasonal allergic rhinitis
SCIT = subcutaneous immunotherapy
SIT = specific immunotherapy
SLIT = sublingual immunotherapy
SMS = symptom-medication score
SS = symptom score

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In Australia, as in other Western countries and increasingly in developing countries, allergic disease is common and places a growing burden on healthcare. The incidence of allergic rhinitis has almost doubled in Australia and New Zealand in the last 15 years. We now have amongst the highest prevalence in the developed world with 16% of the Australian population suffering from the condition.[1] Progression of the disease from infancy to adulthood is poorly understood and previously treatment was almost entirely symptomatic. This presentation by Professor Wahn focused on what is known about the "allergic march", the importance of early intervention, and the potential for secondary prevention. He stressed the importance of understanding the progression of the disease, from the atopic infant through preclinical sensitisation to multiple clinical presentations. Changes to European standards for immunologic therapies in recent years have brought about a large body of research into specific immunotherapy (SIT), providing evidence for potential disease modification. In light of this research, Professor Wahn noted that studies addressing a preventative approach in high risk children in the preclinical state seem to be justified. This review includes some of the highlights from the presentation and a summary of some of the research discussed.

Current immunotherapy; a changing Europe

Immunotherapy to alter allergic disease is not new, but it is changing rapidly. Having lagged somewhat behind many other fields of medicine in the switch from eminence-based to evidence-based medicine, it must now conform to the higher standards of pharmacotherapy. In Europe this takes the form of the recent EMA guidelines for specific immunotherapy (SIT) research under which—depending on study duration—different claims for efficacy are possible:

1. Treatment of allergic symptoms: efficacy in the first pollen season/after some months of treatment.
2. Sustained clinical effect: maintenance of significant and clinically relevant efficacy during two to three treatment years.
3. Long-term efficacy and disease modifying effect: sustained significant and clinically relevant efficacy in post treatment years.
4. Curing allergy: sustained absence of allergic symptoms in post treatment years.[2]

Research used as evidence for these claims should be adequately powered RCT's, using EMA defined primary and secondary endpoints, and must also provide a Paediatric Investigatory Plan for potential application in children. Professor Wahn noted that although the fourth claim is rarely made, there are often a few patients per study who really are cured, and it would be interesting to look at this subgroup in the future.

Specific immunotherapy research

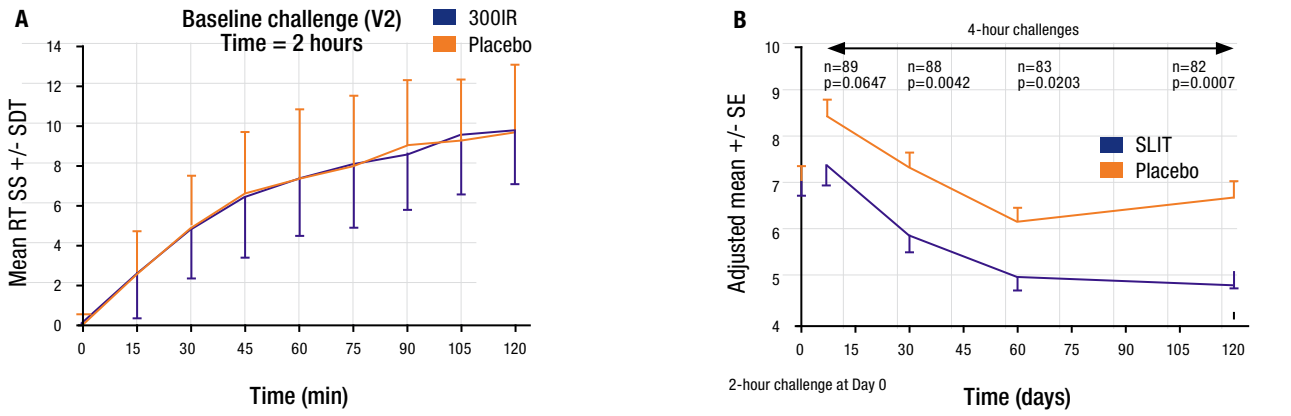
Immunotherapy is not new; in fact it recently celebrated its one hundredth birthday. Over the years the initial ad hoc, eminence-based approach to this field has developed to a highly specified methodology, bringing about a large body of robust supporting evidence. Sublingual immunotherapy (SLIT) and subcutaneous therapy (SCIT) are currently both widely used across Europe, with Professor Wahn quoting figures of 5.5 million patients in total across Europe from 2007 to 2011, with 1.9 million patients being under the age of 18. In grass pollen-related seasonal allergic rhinitis (SARg) we now have documented efficacy in symptomatic improvement (in the first treatment season), sustained clinical effect (for the second and third season) and also in disease modification (after SIT termination). Recently registered SLIT products are supported by a high degree of evidence, and these large RCTs (which include a baseline season) form a benchmark for SIT research. In the future, all studies on SLIT and SCIT should be carried out according to the same criteria.

Research into the use of SLIT for SARg has now been ongoing for several years, allowing time for collection of post-treatment data. One trial found a reduction in rhinoconjunctivitis daily symptom scores of 25% to 36% ($p \leq 0.004$) in the grass allergy immunotherapy tablet group compared with the placebo group over the 5 grass pollen seasons covered in the study, which included two (treatment-free) follow-up seasons.[3] Professor Wahn noted that the difference in seasons could be explained by varying seasonal pollen counts; the higher the pollen exposure of the season, the more likely research is to detect differences between placebo and active treatment. When it comes to paediatric patients sublingual application has obvious advantages over injection-based immunotherapy, and similar data is available for this population. A trial of high-dose SLIT in 207 children aged 4 to 12 years found a change in the area under the curve (AUC) of the symptom medication score (SMS) from the baseline to the first grass pollen season of -212.5 for the active group and -97.8 for the placebo group, ($p=0.0040$).[4] This trial—and others like it—provide confidence to allergists considering the use of immunotherapy in their paediatric patients.

SLIT: onset of action

One method of negating the seasonal variation of pollen counts is to use an allergen challenge chamber, where exposure is controlled within pre-specified amounts. As exposure is strictly time controlled, these chambers also provide the opportunity to study the timeline of treatment effects. Horak F, et al[5] used such a chamber and documented the results, both at baseline and at repeated grass pollen challenges at day 7 and at months 1, 2 and 4. In the baseline challenge all participants developed serious allergy symptoms within minutes of exposure, with maximum effect at the 2-hour mark. In the following challenges the SIT treatment arm displayed a decrease in symptoms compared to placebo, reaching significance after 30 days. These data, shown in figure 1, are in direct contradiction to the general perception of SIT as a long-term plan with very little short-term benefit.

Figure 1. **SLIT onset of action[5]**



Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis[6]

Authors: Didier A, et al

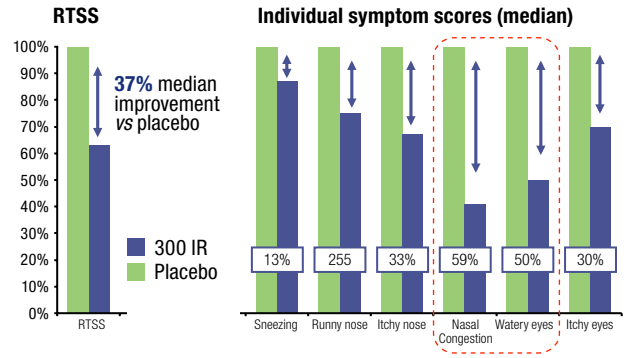
This multinational, double-blind, placebo-controlled study randomised 628 adults with grass pollen rhinoconjunctivitis (confirmed by positive skin prick test and serum-specific IgE) to receive 1 of 3 doses of a standardised 5-grass pollen extract, or placebo, administered sublingually using a once-daily tablet formulation. The treatment was initiated 4 months before the estimated pollen season and continued throughout the season. The primary outcome was rhinoconjunctivitis total symptom score (RTSS); secondary outcomes included six individual symptom scores, rescue medication use, quality of life, and safety assessments. Both the 300-index of reactivity (IR) and 500-IR doses significantly reduced mean RTSS (3.58 ±3.0, p=0.0001; and 3.74 ±3.1, p=0.0006, respectively) compared with placebo (4.93 ±3.2) in the intent-to-treat and per-protocol analyses. The 100-IR group (4.70 ±3.1) score was not significantly different from placebo. Analysis of all secondary efficacy variables (sneezing, runny nose, itchy nose, nasal congestion, watery eyes, itchy eyes, rescue medication usage, and quality of life) confirmed the efficacy of the 300-IR and 500-IR doses. No serious side effects were reported. The authors concluded that—in the first pollen season—the efficacy and safety of SLIT with grass tablets was confirmed.

Optimal dose selection is as important in immunotherapy as it is in pharmacotherapy, with evidence showing varying doses result in marked differences in outcomes. Professor Wahn noted that—in general—a high dose is more efficacious than a low dose, but that the incidence of side effects will usually follow a similar trajectory. Figure 2 shows the efficacy of the 300-IR dose broken down into individual symptom scores, and figure 3 shows the dose response to SLIT therapy, demonstrated by symptomatic and medication scores and reaching a plateau of efficacy. In this case the 300-IR and 500-IR doses both demonstrated significant efficacy compared with placebo, with the risk-benefit ratio favouring the use of 300-IR tablets for clinical practice.

Another variable to be considered is the recommended time to begin treatment, which in the case of SARg is approximately 2-4 months prior to the estimated start of the pollen season. Again, due to the variable nature of yearly pollen counts this research needs to be conducted over several seasons in order to provide a more robust average.

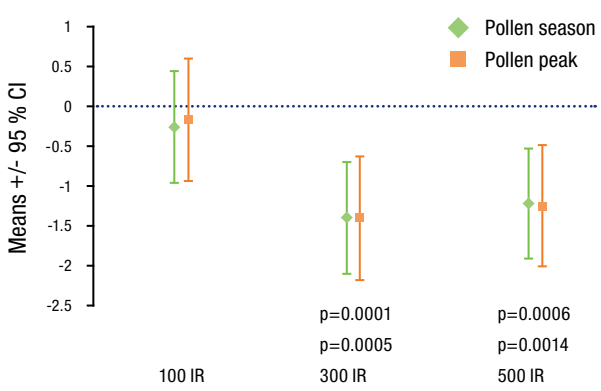
Dose finding studies for SIT are now mandatory in Europe. Despite the additional time and costs involved Professor Wahn commented that this is a very positive step; providing allergists with the information they need to confidently prescribe these treatments. To ensure accurate comparison between products a standardised nomenclature for allergens will need to be applied. Professor Wahn commented that— when considering the concentrations of various SLIT preparations—his experience has been that if you do not get some side effects at the commencement of the treatment, you should question the efficacy of the chosen product.

Figure 2. **SLIT efficacy outcomes on symptom scores**



300 IR tablets have a significant reduction in all symptoms, especially in nasal congestion and watery eyes

Figure 3. **Dose-finding in SLIT**



SLIT: disease modifying effect

There is now a growing body of evidence for the ongoing efficacy of SLIT in post-treatment seasons. A very recent study investigated pre- and co-seasonal SLIT use vs. placebo over three treatment years and one post-treatment season.[7] The active treatment arm was divided into two groups according to initiation of treatment; either 2- or 4-months prior to the start of the pollen season, and the differences in outcomes between these two groups were largely insignificant. In contrast, there were significant differences when compared to placebo; in the fourth (non-treatment) season the least-squares (LS) mean differences in average adjusted symptom score were -1.14 (95% CI, -2.03 to -0.26; p=0.0114) and -1.43 (95% CI, -2.32 to -0.53; p=0.0019) in the 4-month and 2-month groups, corresponding to -22.9% and -28.5% relative LS mean differences (vs. placebo) respectively. The data collected on quality of life showed a similar trend (see figure 4) and shows the benefits of this treatment to be meaningful to patients. Although this is an adult cohort, Professor Wahn noted that this type of research; showing similar results with shortened time-on-treatment, gives cause for hope to paediatric allergists, who are often concerned about compliance.

The allergic march

A key message from Professor Wahn's presentation was the need for a shift in the way we think about childhood allergies. He commented that the baby who presents with eczema will most likely recover, but will present again with asthma five years later. In these patients it is not the skin or the airways that is at fault but the immune system, and a more holistic approach is needed; it is philosophically important to treat the children, not the organs. He noted that it is the right of the child to be taken care of by a clinician who can think systemically, and is aware that—regardless of the transient nature of many individual presentations—the background allergic march is progressing. Historically attempts to intervene and prevent this progression have failed, providing information for future research but little benefit for patients. Now, with increasing evidence that specific immunotherapy can indeed act as prevention for secondary presentations, this message is increasing in relevance; each symptom should not be regarded as trivial or transient, but rather a further step in an "immuno-career" that will last a lifetime.

The Multicentre Allergy Group (MAS) study was a German longitudinal birth cohort study of 1314 newborns born in 1990 and followed for 20 years, the main purpose of which was to describe the natural course of allergic diseases, and to identify risk factors and predictors. The cohort was risk-enriched, with 38% (n=499) having at least one atopic parent, or possessing a high level of cord blood IgE. In 1996 a participant, age 6, presented to the clinic with his first episode of SARg and blood tests revealed allergic sensitisation to Phl p 1, 2 and 4, which would expand to include Phl p 5, 6 and 11 by age ten. Retrospective analysis of study blood samples revealed the first sensitisation (Phl p 1) had taken place three years prior to first presentation, when the patient was asymptomatic at age three. This was not an isolated case in the study; at the age of 3 years, IgE sensitisation predicted SARg by age 12 years (positive predictive value, 68% [95% CI, 50% to 82%]; negative predictive value, 84% [95% CI, 80% to 87%]), and children with sub-clinical sensitisation in early (preschool) age had a greatly enhanced risk of developing SARg within the next 3 years (odds ratio 13.6).[8] See figure 5.

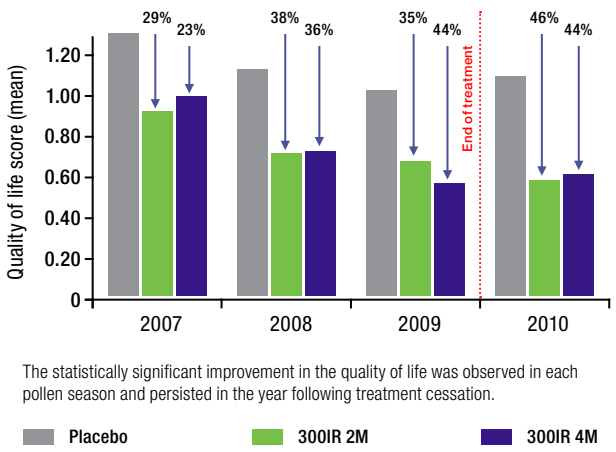
Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children[9]

Authors: Niggeman et al

In a previous trial a 3-year course of SIT in children with hay fever to grass and/or birch pollen significantly reduced the risk of developing asthma. To investigate the long-term preventive effect, this trial performed a follow up 2 years after termination of immunotherapy. A total of 183 children, aged 6-14 years with grass and/or birch pollen allergy could be investigated 2 years after discontinuation of SIT or no treatment. The significant improvement in hay fever and conjunctival provocation tests results observed after 3 years of SIT persisted at the 5-year follow-up. No difference in bronchial responsiveness to methacholine was found after 5 years because of spontaneous improvement during the follow-up period in the control patients. The immunotherapy-treated children had significantly less asthma after 5 years as evaluated by clinical symptoms (odds ratio 2.68 [1.3-5.7] see figure 6) in favour of SIT for prevention of development of asthma and significantly less patients reported an increase in asthma scores (P<0.01).

Professor Wahn noted that although this study was limited by its un-blinded nature (the ethics committee would not allow a placebo injection group), the results clearly indicate the potential for use of SIT as a preventative tool.

Figure 4 **Quality of life[7]**



The statistically significant improvement in the quality of life was observed in each pollen season and persisted in the year following treatment cessation.

Figure 5. **Early sensitisation to grass pollen allergens and probability to be symptom free during consecutive seasons[8]**

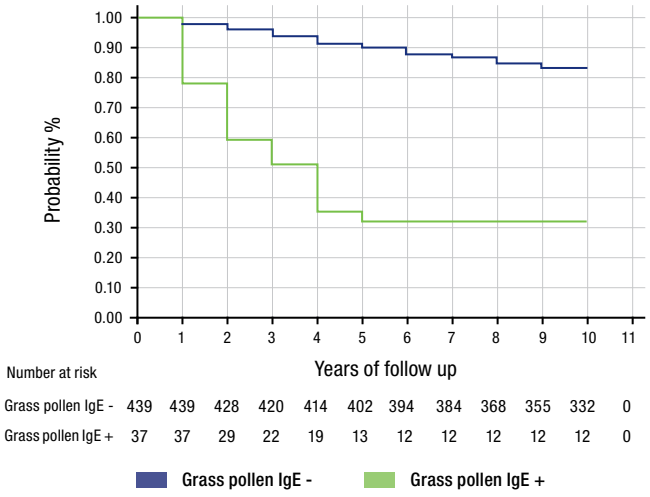
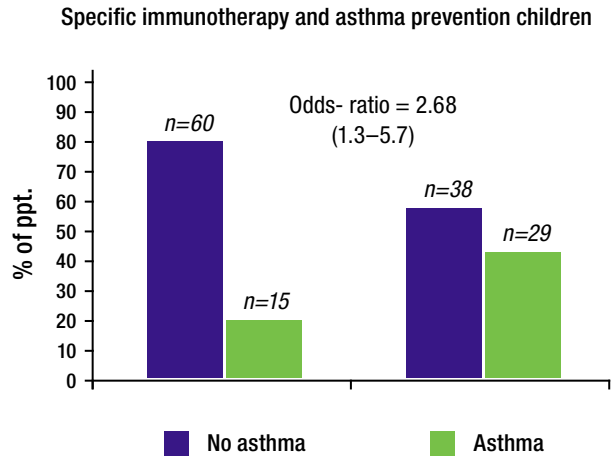


Figure 6. **Development of asthma at 5 years[9]**



Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment[10]

Authors: Holt PG, et al

The trial behind this paper was an example of a prospective preventative trial run in Perth, Berlin, Stockholm and New York and sponsored by the Immune Tolerance Network and the NIH. Although it was stopped due to safety concerns it is a model of the very trials Professor Wahn believes are so important to allergy research, into the earliest stages of the disease. This paper promotes new thinking about preventative approaches—particularly the role of viruses, which are so crucial in the early stages of allergy, often triggering the initial development. Not only is immunotherapy suggested in established disease, but also as "immuno-prophylaxis" for primary prevention. Professor Wahn described this as a fascinating area of research, and hopes research such as this will be able to demonstrate whether, at a very early age, there is disease modifying potential for disease prevention.

Other prospective birth cohort studies tracking asthma initiation and consolidation in community cohorts have identified viral infections occurring against a background of allergic sensitisation to aeroallergens as a uniquely potent risk factor for the expression of acute severe asthma-like symptoms and for the ensuing development of asthma that can persist through childhood and into adulthood. A combination of recent experimental and human studies have suggested that underlying this bipartite process are a series of interactions between antiviral and atopic inflammatory pathways that are mediated by local activation of myeloid cell populations in the airway mucosa and the parallel programming and recruitment of their replacements from bone marrow. Targeting key components of these pathways at the appropriate stages of asthma provides new opportunities for the treatment of established asthma but, more crucially, for primary and secondary prevention of asthma during childhood.

The future of allergy

Professor Wahn stressed that it is time for a change in the way we think about paediatric allergy. In this new era the days of patient-specific, eminence-based treatment are over, replaced by a burgeoning supply of robust research. He remarked that there could hardly be a more exciting field of medicine right now, not only because of the wealth of evidence emerging to support current treatments, but also due to the possibilities for a whole panel of new approaches. As well as the SCIT and SLIT discussed there are also other delivery methods being developed including oral, nasal and lymphatic delivery, among others. He noted that current early allergy diagnosis may not be sufficient as it starts after onset of symptoms, and urged the audience to think beyond these limits and start to consider "immuno-prophylaxis"; intervention at the very start of the allergic process to prevent disease development. His final recommendation was that as immunotherapy is the only current treatment with proven disease modifying potential, studies addressing a preventative approach in high risk children in the preclinical state are needed to evaluate the potential for future use in this cohort.

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In 1971 Professor Wahn began his career as a doctor at the University Clinic in Heidelberg. He later became an academic employee at the German Cancer Research Centre in Heidelberg, and a medical specialist in Paediatric Allergology and Paediatric Pneumology. He was scholarship holder of the Deutsche Forschungsgemeinschaft (DFG) at the National Institutes of Health (Clinical Immunology Section) in Bethesda, Md., USA. From 1981 until 1985 he was senior physician at the Paediatric University Clinic in Bochum as well as assistant Professor at the Ruhr University Bochum. Since 1986 he has been Professor of Paediatric Pneumology and Immunology at the Paediatric Department, Free University, Berlin as well as Chief Physician of the children's' department at HELIOS Hospital Emil von Behring. From 1998 – 2012 Professor Wahn was director of the clinic for Paediatric Pneumology and Immunology at the Charité Hospital in Berlin and from 2011 – 2012 he was also appointed director of the Laboratory Section Allergology/Immunology in Berlin.

Professor Wahn served as President of the European Academy of Allergy and Clinical Immunology (EAACI) from 2003 – 2005. He has been president of a variety of national and international Congresses and was appointed as Chief Editor of the journal *Pediatric Allergy and Immunology* in 2010. His research interests include the epidemiology of asthma, predictive factors of allergy and allergy prevention. He has published over 450 articles in first line international journals and more than 30 textbooks in different languages.

Professor Wahn received an honorarium to give a lecture at this meeting.
Stallergenes also granted funding for this publication.

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