

Lecture Reviews



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The role of nutrition in epidemiology of allergy



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Background

The expression of allergic diseases may vary with age, and symptoms may disappear and be replaced by other symptoms. In infancy, the main symptoms are atopic dermatitis, gastrointestinal symptoms and recurrent wheezing, whereas asthma and allergic rhinoconjunctivitis are the main problems later in childhood. Adverse reactions to foods are most common in the first years of life, whereas allergy to inhalant allergens mostly occurs later. It is therefore important to be aware of the natural course of allergic diseases when evaluating different factors that may play a role in the epidemiology. The development of an allergic disease depends upon a complex interaction between genetic and several environmental factors. Thus, many different factors may contribute to the increase in the prevalence of these diseases. Many interesting hypotheses as regards possible causal relationships have been raised, but so far most of these remain to be documented.

Key message

Breast feeding and late introduction of solid foods are associated with a reduced risk of acquiring food allergy, especially cow's milk protein allergy and atopic dermatitis. In prospective, randomised studies, a preventive effect of feeding high-risk infants exclusively with an extensively hydrolysed formula for the first 4-6 months of life as regards development of food allergy and atopic dermatitis has been documented. Some studies indicated a preventive effect of breast feeding regarding recurrent wheezing and early childhood asthma, but results of different studies are conflicting and at present there is no convincing documentation for a preventive effect as regards inhalant allergy. Recent studies indicated that variations in the composition of human milk might partly explain some of the controversies regarding the protective effect of human milk.

The results of cross-sectional studies suggest that dietary factors such as low intake of fresh fish, omega-3 fatty acids, high sodium intake or inadequate intake of antioxidants may influence respiratory symptoms and asthma. Recently, clinical research has shown an increased prevalence of obesity and higher body mass index among

asthmatic children. It is unclear whether obesity or metabolic factors influencing obesity may cause asthma, or whether asthma and reduced physical activity may cause obesity.

Summary

Several prospective studies have shown an association between exposure to food allergens during the first 4-6 months of life and the development of food allergy and atopic dermatitis. In high-risk infants exclusively breast feeding or feeding an extensively hydrolysed formula is shown to result in a reduced risk of food allergy. As regards development of inhalant allergy, studies have shown conflicting results and no firm conclusions can be drawn. Prospective longitudinal studies are needed to elucidate the possible cause/effect relationship between dietary factors, obesity and asthma.

Conclusion

Exposure to food allergens in infancy plays a role for the development of food allergy, but at present there is no documentation for an effect as regards development of inhalant allergy. The possible importance of other nutritional factors remains to be documented in prospective longitudinal studies.

The role of infectious diseases in epidemiology of allergy



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The results of recent studies substantiate the potential protective effect of infections early in life on the development of mainly atopy and to a lesser extent on asthma in later childhood. In Guinea-Bissau, West Africa, Shaheen and colleagues followed children at the age of 0-6 into young adulthood. The subjects with childhood measles had about half the rate of atopic sensitisation defined as positive skin prick test to aeroallergens than those who had been vaccinated and did not acquire measles (12.8% vs. 25.6%). A recent report from Southern Italy showed that military recruits who were serum positive to hepatitis A as a potential indicator of hygiene had a significantly lower prevalence of atopic sensitisation to common aeroallergens and a lower prevalence of atopic diseases as compared to their peers, who did not have antibodies to hepatitis A. In a recent study from East Germany, the development of allergy at the age of 5-14 was significantly reduced if a child from a small family entered day nursery between 6-11 months of age, as compared to children 12-23 months of age or after the second birthday (15.7% vs. 21.8% vs. 27%). In the prospective Tucson Cohort Study, children who had non-wheezing lower respiratory tract illnesses such as pneumonia and tracheobronchitis in their first three years of life had subsequently reduced skin test reactivity and depressed levels of total serum IgE at the age of 6. A potential protective effect of parasitic infections, e.g. in areas of the developing world has not yet been explored sufficiently. Microbial stimulation both from normal commensals and pathogens through the gut may be another route of exposure, which may have altered the normal intestinal colonisation pattern in infancy. Thereby the induction and maintenance of oral tolerance of innocuous antigens such as food proteins and inhaled allergens may substantially be hampered. These hypotheses, though intriguing, have to date not been supported by epidemiological evidence since significant methodological difficulties arise when attempting to measure the microbial pattern of the intestinal flora.

A "human model" which may prove interesting in this context is the recent observation reported by several authors that growing up on a farm confers significant protection against the development of atopy. In a Swiss population of 6-15 year old schoolchildren, the odds of having seasonal symptoms of hay fever (adj. OR=0.34, 95% CI: 0.12-0.89) and of developing atopic sensitisation as measured by RAST (adj. OR=0.31, 95% CI: 0.13-0.73) were strongly decreased in children raised on a farm as compared to their peers from the same rural area whose parents were not farmers. Similarly, in a large survey of Bavarian children entering school at the age of 5-7, the prevalence of hay fever among children raised on a farm was significantly lower than among their peers from the same villages, who did not grow up on a farm (1.8% vs. 4.9%, $p \leq 0.001$). Adjustment for potential confounding variables confirmed the strong inverse relation (adj. OR=0.52, 95% CI: 0.28-0.99). A recent Austrian survey of 8-10 year old children has confirmed the findings. In all surveys a slightly protective effect was also seen for the prevalence of asthma (e.g. adj. OR= 0.65, 95% CI: 0.39-1.09 in Bavaria), whereas the development of atopic eczema was not affected by farming activities of the parents.

The role of environmental pollution in epidemiology of allergy



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Allergic diseases and sensitisation are increasing in western industrialised countries. It had been hypothesised that environmental pollution might be partially responsible for this increase.

Pollution from sulphur dioxide (SO₂) or total suspended particles (TSP) cannot explain the increase, since East-West comparison studies in Europe show lower prevalence of allergies in eastern areas where this type of pollution is much higher. Additionally, allergies in East Germany are increasing while SO₂ and TSP pollution is decreasing. This is one result from our yearly repeated cross sectional studies in differently polluted areas in East Germany and in three differently polluted areas in West Germany. Between 1991 and 2000, about 35000 six-year-old children participated. We found a significant association of SO₂ and TSP with infectious airway diseases in East Germany, and the decrease in these pollutants has already had a favourable effect. An effect of SO₂ or TSP pollution on allergies or sensitisations could not be detected.

Traffic pollution is the main source of air pollution in western industrialised countries. There is experimental evidence that traffic related pollution and especially diesel exhaust particles may enhance sensitisation and provoke symptoms of allergic diseases. Additionally, this type of pollution may alter pollen properties, as we could show in several experiments. Some epidemiological studies found an association between the amount of traffic at the living place of children with symptoms of allergies and allergic diseases. We found an association of allergies and related symptoms and sensitisation to traffic related outdoor NO₂, which probably was a proxy for outdoor-small-particle concentration. This effect could only be seen in parts of cities with the highest amount of traffic.

Effects of traffic related pollution probably only explain a small part of the increase in allergies, and other factors like lack of microbial stimulation in early childhood have to be considered too. Yet its effect is relevant for a lot of people living in the cities with great consequences for public health.

Primary allergy prevention



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Prospects of primary prevention of childhood allergy

The reasons for the pronounced increase in the incidence of allergic diseases in industrialised countries are unknown. The increase is most obvious in children and young adults, and it appears to be a consequence of events encountered rather early in life. So far, the avoidance of any of the numerous suggested risk factors has at best only had marginal effects on the prevention of the allergic march. Despite the lack of clinical and experimental support, allergy preventive measures are often recommended. Prospective clinical studies, carefully performed analyses of epidemiological data and experimental investigations over the past several years indicate that there is little support for any of the recommendations.

Reduction of early exposure to inhalant allergens

is still often recommended. This was based on the observation that asthmatic children are often sensitised at an early age, and that early exposure to high levels of allergens is often associated with a positive skin prick test. The explanation is probably that atopic individuals are often sensitised, but this has no direct connection with the disease. On the contrary, recent studies indicate that exposure early in life may indeed protect against allergy to that allergen later in childhood and adulthood.

Breast feeding is of major importance for child health globally, and there are many good reasons for breast feeding also in industrialised countries. Breast feeding is associated with a lower incidence of wheezing in infancy. This is due to the anti-infective properties. There is limited support however for any protective effect against allergy. Any observed effects that were reported in studies 20-30 years ago may have been indirect and not directly related to the breast feeding.

Poor **indoor** air quality has also been suggested as a risk factor. While this may partly be true for infantile wheezing, there is little support for this regarding allergy. This is to some extent true also for exposure to **tobacco smoke**. While there is little doubt that tobacco smoke is the major indoor air pollutant and is a major contributory factor to

wheezing in infants and young children, a cause-relationship with allergic disease is more questionable.

In conclusion, there is not enough scientifically documented advice for allowing any recommendation for allergy prevention in general. The avoidance of cow's milk protein in early infancy may however prevent cow's milk allergy. As the prevalence in infants is only about 2%, and cow's milk allergy is uncommon later in life, such advice, even if given to the general population, would only have a modest effect on the incidence of allergy, nor would it prevent the development of other allergies.

It is possible that allergy prevention in the future can be based on various forms of immunomodulation, including modifying the microflora. Clinical studies exploring such novel strategies are ongoing or in the planning stage. Until solid scientific information is available, it would appear unethical to continue currently given advice for primary prevention of allergy, such as avoidance of exposure to inhalant allergens, whether it is given to the general population or to selected so-called allergy risk groups, i.e. infants with a family history of allergy.

Primary allergy prevention



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Targeting immunological events in early childhood

It is clear from studies in adults that atopics and non-atopics express reciprocal patterns of T-cell immunity to inhalant allergens. The typical pattern of cytokine expression by allergen-specific Th-memory cells in atopics involves production of the cytokines IL-4, IL-5, IL-9 and IL-13, often accompanied by IFN γ , in contrast to low level production of IFN γ together with IL-10 in non-atopics. Hence the key issue in relation to primary prevention of allergy is how generations of these alternate patterns of Th-memory can be controlled.

The applicability of the Th1/2-paradigm to this problem continues to be debated, as more information becomes available on the precise patterns of Th-cell responsiveness in atopics and non-atopics, and on the role of different populations of “regulatory” T-cells which control Th-cell differentiation. Recent studies from our laboratory demonstrating reciprocal patterns of allergen-induced expression of Th2-associated Transcription Factors in T-memory cells from atopics and non-atopics are consistent with the broad applicability of the model. However, it is becoming evident that additional layers of regulation extrinsic to Th1/Th2 cells themselves are also operative, which help to determine the ultimate nature of allergen-specific T-cell memory. These involve environmental factors such as microbial stimulation and host factors related to the functions of antigen present cells and to different populations of specific/non-specific T-regulator cells, particularly those functioning at mucosal surfaces.

Research into the kinetics of inhalant allergen-specific Th-memory generation in humans has produced convincing proof that in a high proportion of subjects programming of long-term memory occurs during early childhood. Studies on the cellular and molecular mechanisms underlying allergen-specific Th-memory generation have demonstrated that genetic risk for development of Th2-like memory is associated with delayed postnatal maturation of Th1-competence, measured as capacity to secrete IFN γ in response to polyclonal stimuli. The precise mechanism(s) underlying this

maturation delay await definition, but may include variations in capacity to respond to Th1-stimulatory signals from the microbial environment due to polymorphism(s) in the CD-14 gene and possibly variations in the levels of methylation of the IFN γ promoter, which directly controls transcription of the IFN γ gene. It is not yet established whether risk of atopic sensitisation in this context is a direct consequence of reduced IFN γ production, or whether this is a surrogate marker for a more fundamental underlying deficiency in Th1-function such as IL-12 which is also developmentally regulated, and research into this important question continues.

It is additionally clear from studies on human T-cells and from experimental models, that Th-cell responses are initially plastic but become progressively less susceptible to redirection down alternate differentiation pathways with repeated cycles of boosting. Accordingly, the most likely “window” for successful immunological control of allergen-specific Th-memory development would appear to be in childhood, during the period when the natural Th-memory programming process is still ongoing. An increasing range of theoretical approaches can be contemplated in this context, including:

- various forms of allergen-specific immunotherapy, alone or in conjunction with immunomodulators, targeted at selected downregulation of Th2-functions or upregulation of Th1-functions
- administration of selective Th2-antagonists alone, enhancing the normal development of more Th1-like patterns of memory which is driven by passive exposure to environmental allergens
- elective boosting of Th1-functions.

The potential risk/benefit relationships inherent in each approach merit careful evaluation.

Primary allergy prevention



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Background

The development and phenotypic expression of allergic diseases depend upon an interaction between genetic factors, environmental exposure to allergens (food and inhalant allergens) and many other environmental factors such as tobacco smoke, air pollution, infections, and possibly also dietary factors and intestinal microbial flora/probiotics. It is estimated that genetic factors account for around 50% of asthma and allergy cases. Many children who develop an atopic disease, particularly recurrent wheezing and asthma in early childhood, do not belong to high-risk groups (at least one first relative with doctor-diagnosed atopic disease). Thus, some preventive measures may be beneficial to the general population and supplementary measures may be beneficial and recommendable only to high-risk individuals.

Key message

- The study design of studies on primary allergy prevention, both non-interventional and interventional studies, should be prospective and include: Well-defined diagnostic criteria and outcome measures, sufficient duration of follow-up, proper sample size for adequate statistical evaluation, blinding and control for confounders, registration of compliance and follow-up on drop outs.
- Randomised, controlled studies are required to demonstrate causative mechanisms and effect of elimination/prevention of the causative factors.
- Prospective non-interventional studies are useful to generate hypotheses.
- Retrospective and cross-sectional studies are not suitable for assessment of cause/effect relationship between exposure to allergens/adjuvant factors and development of allergic disease.

Summary

Prospective non-interventional studies have shown a clear association between exposure to indoor allergens and sensitisation, as well as a clear association between sensitisation and development of asthma has been documented, especially in high-risk infants. However, no significant direct

association between early exposure to indoor allergens and development of asthma up to the age of 7 has been documented. Importantly, such an association should only be expected as regards allergic asthma. A relationship between prenatal as well as postnatal exposure to tobacco smoke and the development of asthma and increased morbidity in asthmatics has been documented. Early feeding, breast feeding and late introduction of solid foods (≥ 4 months) are associated with a reduced risk of food allergy, atopic dermatitis and in some studies also a reduced risk of recurrent wheezing and asthma. Prospective, randomised, interventional studies have documented that exclusive breast feeding or documented hypoallergenic formulas for the first 4-6 months of life in high risk infants cause a reduction of the incidence of food allergy (especially cow's milk allergy) and atopic dermatitis during the first 5-7 years of life.

Conclusion

Evidence-based recommendations for primary allergy prevention:

For all infants:

- No special diet during pregnancy or for the lactating mother
- Exclusively breast feeding for at least 4 months
- Avoidance of solid food until 4 months of age
- Avoidance of exposure to tobacco smoke, also during pregnancy

For high-risk infants, further recommendations:

- If supplement is needed during the first 4 months, a documented hypoallergenic formula is recommended
- Reduced allergen exposure early in life, (house dust mites, furred pets, cockroaches).

Secondary Allergy Prevention



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A relevant increase in prevalence of childhood asthma and other allergic diseases have been documented in the last three decades, both in industrialised and in developing countries, with an evidence for a more direct role of the indoor allergens (1).

The most important environmental risk factor in connection with childhood asthma in many countries belonging to the temperate zone is house dust mite sensitisation (2).

While several studies have been performed evaluating the effectiveness of indoor allergen reduction in primary and tertiary allergy prevention, very few studies have focused on secondary prevention.

HDM sensitivity can be lost as well as acquired by environmental change. In a study including 115 children with positive skin prick tests to mite allergens, 67 became skin prick test negative over a period of 2 years, and 48 remained skin prick test positive. As many as 66 out of the 67 subjects whose skin prick responses became negative during this period were exposed to a concentration of mite allergen less than 2 µg/g dust. A total of 15 of the 48 who remained skin prick test positive had a level of exposure greater than 2 µg/g dust (3). The possibility that this outcome could be associated with the prevention or remission of asthma, by analogy with occupational asthma, needs to be tested in long-term, randomised, controlled studies.

There is only one study which evaluated the effect of mite antigen manoeuvres in subjects with specific IgE for mite, but not yet diagnosed as asthmatics. In these adult subjects (4), the use of mattress covers for 6 weeks was associated with a significant improvement in symptom scores for disturbed sleep, breathlessness and wheezing compared to the placebo group (5). These findings are at variance with others in the same group, when talking about very mild asthma (6). Larger studies with a longer follow-up period are necessary.

Antigen avoidance is often recommended for dust mite sensitive asthmatic children, as part of an overall therapeutic strategy (tertiary intervention).

We need more studies in primary and secondary prevention.

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Secondary allergy prevention



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Development of allergy often follows a typical pattern, named the allergic march (1), with atopic dermatitis in infancy, asthma or allergic rhinitis during pre-school and school age. Secondary allergy prevention concerns the prevention of further allergy development after the first symptoms have occurred, e.g. development of asthma after atopic dermatitis or development of asthma after the first symptoms of wheezing.

Secondary allergy prevention may consist of environmental precautions, dietary precautions and different types of medical treatment.

Studies on environmental control and dietary intervention have mostly been assessed as primary prevention in relation to high-risk children and have demonstrated to some extent to delay the development of allergic symptoms and allergic sensitisation (2-4).

Several approaches have been tried with pharmacotherapy as part of secondary allergy prevention. Antihistamines were tried out in infants with atopic eczema and early wheezing. Promising results were demonstrated with ketotifen as compared to placebo in a randomised, double blind study of infants with atopic dermatitis on the development of asthma (5). In infants with early wheezing and a family history of atopy, similar results were found with ketotifen upon development of asthma (6). Later a large-scale international randomised, placebo controlled study (ETAC) assessed the effect of cetirizine on the development of asthma in infants and young children with atopic dermatitis. It was found that asthma development was less frequent in cetirizine treated children with grass pollen and house dust mite allergy (7).

It has been found that inhaled steroids may have an effect on symptoms in infants with early wheezing after bronchiolitis (8-9). Reijonen et al. described that inhaled budesonide and inhaled disodium cromoglycate had a beneficial effect on early symptoms after acute bronchiolitis (10), but four months' treatment did not have any effect (11).

Allergic rhinitis is followed by asthma in many patients. Anti-inflammatory treatment of allergic

rhinitis has been found to influence bronchial responsiveness (12), but it is not known if there is an effect on later asthma. Preliminary results suggest that allergy vaccination in children with allergic rhinitis may protect against development of asthma in allergic children (13-15).

The accumulating increased knowledge about allergic inflammation and the genetics of allergic diseases may lead to the development of novel measures for the prevention of allergic diseases.

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Secondary allergy prevention



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Indoor allergen exposure has been shown to be associated with specific sensitisation in atopic individuals (Lau 1989, Wahn 1997). Furthermore, sensitisation to indoor allergens has been found to be a major risk factor for the development of childhood asthma. However, longitudinal studies have shown, that there is no direct relationship between childhood asthma and indoor allergen exposure (Lau 2000). Some authors speculate that high pet allergen exposure in early childhood might prevent children from acquiring allergy and asthma later (Platts-Mills 2001). However, allergen avoidance studies were successful in reducing bronchial hyperresponsiveness in sensitised asthmatic individuals as a strategy of secondary and tertiary prevention.

A number of intervention studies are currently being performed in cohorts followed prospectively from birth, examining the effect of indoor allergen elimination on the incidence of asthma (for example the Manchester Asthma and Allergy Study MAAS [Custovic 2001]). The results will clarify whether it is meaningful to consider indoor allergen elimination an important element of primary prevention of various atopic manifestations. But even if it turns out that other factors play a major part in determining whether an atopic child will develop asthma, so that allergen elimination as a measure of primary prevention is inefficient, a reduction of allergen exposure will still remain a very important element in secondary and tertiary prevention, as shown in a trial on mite-proof encasings (Ehnert 1992).

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Psychological factors and hypersensitivity – results from experimental studies



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Psychoneuroimmunological research in the last two decades has revealed a number of bi-directional interactions between the central nervous system (CNS) and the immune system, including “hard-wired” neural connections and shared recognition molecules and receptors. In addition, results from a growing number of studies have shown associations between a range of psychosocial factors, e.g. stress and negative emotional states, and a number of quantitative and functional immune measures, e.g. white blood cell counts, natural cytotoxicity, and proliferative responses. These results suggest that immune and inflammatory processes, including immediate (ITH) and delayed type hypersensitivity (DTH) reactions, may be influenced by the “mind”. The majority of experiments studying the influence of psychosocial factors on ITH and DTH reactions have focused on the effects of hypnotic suggestions (1).

Experiments studying the effects of hypnotic suggestions on ITH have either studied inflammatory skin reactions in allergy patients or used histamine as inducer of ITH-like reactions in healthy subjects. In one study, healthy subjects were given suggestions to simultaneously imagine the reaction to a histamine prick test increase in one arm and decrease in the other. When compared to a control condition, a significant decrease in the flare reactions was found in the relevant arm, while no significant effects were found for the suggestions to increase the reaction.

In another study, healthy subjects were given suggestions of hypnotic analgesia in one arm. A significant decrease in the flare reaction, compared to the control condition, was found in the analgesic arm, but not in the control arm. The results of a study investigating the effect of hypnotic suggestions to enhance and suppress the inflammatory skin reaction to UVB-irradiation of the skin suggest that the influence on histamine reactions are likely to be mediated by the ability of the subjects to modulate local cutaneous blood flow. In a recent experiment, histamine flare reactions increased during a condition of hypnotically induced sadness, compared to during a hypnotic condition of happiness, lending support to findings of more allergies in depressed individuals. Unlike

ITH, DTH reactions, e.g. the so-called Mantoux or tuberculin skin test, are mediated by specific T-cells, and have shown to be useful *in vivo* measures of immunocompetence. In one study, healthy subjects were given suggestions to simultaneously enhance the reaction to tuberculin (PPD) in one arm while suppressing the reactions in the other. Significant differences in the expected direction were found after 48 h, while no differences were found in a control group. In a double-blinded study, healthy volunteers were sensitised with experimental allergens (DCP and DNCB) and given hypnotic suggestions in the sensitisation phase to enhance the reaction to one allergen and suppress the reaction to the other. During the challenge six weeks later, no hypnotic suggestions were given. The results showed significant differences in DTH reactions in the expected direction, suggesting that psychological influence during sensitisation may affect the later DTH reaction to the challenge.

Results from other studies indicate that the ability to influence the DTH reaction depends on the dosage and type of antigen used. While effects on specific reactions can be observed, the mediating mechanisms may still be non-specific.

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The natural history of allergy



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In the majority of cases, atopic sensitisation becomes manifest during infancy. The first IgE-responses are directed towards hen's egg and cow's milk allergens. IgE-responses to indoor and outdoor inhalant allergens are rarely detected in infancy but develop during the first 10 years of life. IgE responses to hen's egg can be considered to be the earliest serological marker for atopy and are an important predictor of subsequent sensitisation to inhalant allergens. Children who switch from infantile responses to food proteins to subsequent IgE responses to aeroallergens are at risk of developing chronic airway diseases, particularly asthma.

The first clinical manifestation in atopic children is atopic dermatitis, which is prevalent in about 10% of children at age 1. During the first 2 years of life, recurrent wheezing is primarily triggered by infectious agents and is related to atopy in only a small subgroup. However, in the third year of life on sensitisation to indoor and outdoor allergens, it becomes a risk factor for the manifestation of upper and lower airway symptoms.

Seasonal allergic rhinoconjunctivitis may develop from the third pollen season of life. By the school age it has become the most prevalent atopic phenotype, which is accompanied by asthma wheezing in more than 40% of all children.

The united airways - theoretically



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It is logical to consider the airways as one unit from the tip of the nose to the alveoli. There are similarities and differences between the upper airways (the nose) and the lower airways (the tracheobronchial tree).

While the nose is a double-tube, open in both ends, the tracheobronchial tree consists of a branching system, only open proximally. As a consequence, secretions can easily be removed from the nose, while viscous secretions may plug the lower airways. Otherwise the secretory apparatus seems to be the same throughout the airways, and we cannot explain why the nose, and not the lower airways can produce large amounts of watery secretions. The existence of a few hundred large serous glands in the anterior part of the nose is probably of importance.

While the surface and the glandular epithelium, as well as the cells of lamina propria, seem to be the same throughout the airways, a major difference is the existence of venous sinuses in the nose (causing nasal blockage) and of smooth muscles in the bronchi (causing bronchoconstriction).

Another major difference is the degree of environmental exposure. While the nose constantly is influenced by polluted, allergen-containing air of unphysiological conditions, the bronchi are far less exposed due to the protection yielded by the nose - unless of course stupid people directly inhale smoke through the mouth.

Stimulation of sensory nerve fibres in the nose will result in sneezing and rhinorrhoea while it in the lower airways predominantly causes coughing and bronchoconstriction. While cold and polluted air will induce reflex-mediated symptoms in all noses, even ordinary indoor air may induce reflexes in hyperreactive rhinitis noses.

In allergic airway diseases, histamine is a potent inducer of reflex stimulation, resulting in sneezing and in bronchoconstriction, but histamine and other mediators also have a direct effect on smooth muscles in vasculature and in bronchi. While leukotrienes play a major role in the bronchi, their effect in the nose is insignificant, limited to slight changes in blood vessels.

Allergens, in particular large-size allergens (pollen grains, mite faeces), are predominantly deposited in the nose, which acts as a filter for inhaled air. This means that antigen presentation mainly takes place in the nose whether the patient suffers from rhinitis, asthma or both. Antigen-presenting Langerhans cells travel from the nasal mucosa to the regional lymph nodes and the adenoids, where T-cells are stimulated. It is not known whether the stimulated T-cells home exclusively in the nose or whether they also travel to other parts of the airway mucosa.

The effector cells of allergic inflammation, mast cells, Th2 cells and eosinophils seem to play the same role throughout the airways. While allergic inflammation in the lower airways results in epithelial destruction, the epithelial lining is intact in allergic rhinitis.

A holistic view of the airways as one immunological and inflammatory unit, "The United Airways", may probably lead to a better understanding of disease pathophysiology and to new therapeutic concepts. As an example of immune-inflammatory interaction between upper airways and the circulation, we have recently shown that intranasal steroid treatment in pollen-allergic patients completely blocks the activation of circulating eosinophils during the pollen season. One can advance the hypothesis that inhalant allergy is best treated with nasal inhalation of a steroid molecule deposited in the entire airway, similar to the deposition of the allergen particles. We have found that nasal inhalation of budesonide through a spacer have a good effect on both allergic rhinitis and asthma.

The united symptoms - clinically



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During several decades, allergic asthma and allergic rhinitis have increased simultaneously in prevalence.

The reason behind this increase is unknown, and opinions are sometimes opposing. Some specialists believe that we are exposed to too much pollution and allergens, whereas others claim that we are living much too clean and do not develop our immune system normally. Allergy is a systemic alteration in the immune response. Asthma and rhinitis have a strong connection and coexist in many patients. In total, 85% of patients with allergic asthma have manifestations of allergic rhinitis, and almost all have signs of allergic inflammation in the nose. About 20% of the patients with allergic rhinitis have asthma and bronchial hyperresponsiveness simultaneously. The question is if the two clinical diseases are separate and independent manifestations of allergy, or if asthma and rhinitis are closely linked pathophysiologically, and interactions between the nose and the bronchi are of clinical importance.

It is known that the presence of allergic rhinitis is a risk factor for asthma development by a factor 2-3. Some few studies have addressed the question: Can pharmacological treatment with antihistamines, corticosteroids or immunotherapy prevent the development of asthma in rhinitis patients? The results from the PAT-study indicate such a protection from injection immunotherapy in children regarding pollen allergy and development of bronchial hyperresponsiveness. To elucidate the interaction between upper and lower airways, clinical studies of especially the influence of corticosteroids on upper or lower airways when given to the alternative organ have been performed. It was observed that lung symptoms and bronchial hyperresponsiveness accompanied deterioration in for example allergic rhinitis symptoms. It was found initially that nasal corticosteroids would improve symptoms from the lower airways and protect against bronchial hyperresponsiveness. In fact a better protection of the lungs was in one study found when the drug was given via the nose. A similar study in patients with asthma and rhinitis found that corticosteroids given locally to the lung improve the nasal manifestations, but that could be attributed to systemic absorption and activity of the drug. A recent placebo controlled study with corticosteroids given to the lung and/or the nose gave a similar result.

It seems that allergy as a systemic alteration in the immune response with IgE production sensitises any skin or mucosal organ, and that local regulatory functions combined with this chronic abnormality can give rise to clinical disease. The evidence today is that allergic asthma and rhinitis is a common manifestation of allergy, whereas a direct reflex mechanism (neurological, immunological) is not of clinical importance.

Physically nasal patency is important for the breathing pattern, and nasal obstruction will make mouth breathing necessary. This can theoretically lead to a higher exposure of the lungs to allergens and pollution because the nasal filter is bypassed.

There is obviously indirect interaction between nose and lung in allergic disease manifestations. But the common cause of the allergic diseases is the immunological alterations including specific IgE antibody production. Several pharmacological treatments have influence on the allergic reaction in the lung and in the nose. In that way the treatment of one organ can lead to improvement in the other because of systemic activity. The same argument is applicable to immunotherapy that addresses the immunological response in a general manner.

It is possible that different genetic factors promote allergy and others the resistance to specific organ manifestations. The environmental allergic sensitizers and different substances with adjuvants effects or development of allergy and respiratory diseases must be identified for proper primary prevention and disease control.

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One, two, three, many allergies



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Increases in prevalence of allergic respiratory diseases in children have been reported in most westernised countries. Little is known about similar trends in the adult population in these countries, although the increased disease prevalence in children should now also appear in adults. The Copenhagen Allergy Study (CAS), a population based study of allergy in adults, has shown an increase in the prevalence of allergic respiratory diseases in adults in Copenhagen during the 1990s. A corresponding increase in the prevalence of specific IgE sensitisation in particular multi-sensitisation to common inhalant allergens supports the interpretation that the increase in disease prevalence is real and is not merely due to increased recognition. The increase in multisensitisation may partly explain a concomitant increase in morbidity among allergic patients, i.e. sensitised subjects are more likely to experience respiratory symptoms on exposure to specific allergens.

In a cohort of adults examined at two occasions 8 years apart, sensitisation at baseline was the strongest risk factor for the development of new sensitisations such as sensitisation to animals. The more different sensitisations at baseline the greater the risk of developing new sensitisations to animals (“One, two, three, many allergies”).

Furthermore, in the same cohort, pollen asthma appeared to be almost non-existent without in addition pollen rhinitis, and pollen asthma developed only in subjects who had pollen rhinitis at baseline or developed pollen rhinitis during the study period. These epidemiological data support the hypothesis that rhinitis and asthma are one disease entity when both related to specific pollen allergy.

Thus, the natural course of allergic respiratory diseases in adulthood is not necessarily associated with spontaneous regression of disease with increasing age. Therefore, efficient measures for secondary prevention are needed.

In summary, results from the CAS indicate that

- allergic respiratory disease is increasing in adults
- an increase in multisensitisation and morbidity seem to have occurred
- sensitised subjects are at increased risk of developing more sensitisations
- allergic rhinitis and allergic asthma are one disease entity
- allergic rhinitis patients are at increased risk of developing allergic asthma.

Specific allergy vaccinations



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Allergic rhinitis, although often trivialised, is an important cause of morbidity and impaired quality of life. Allergic rhinitis and asthma frequently coexist and rhinitis is a risk factor for the development of bronchial asthma. Allergen immunotherapy is indicated in patients with IgE-mediated disease, a limited spectrum of allergies and failure to respond to conventional treatment with antihistamines and topical corticosteroids (1). We previously showed that allergen immunotherapy was highly effective in patients with severe summer hayfever unresponsive to conventional anti-allergic drugs (2), and treatment for 3-4 years resulted in long-term benefit for at least up to 3 years following discontinuation of treatment (3). The mechanism of immunotherapy is likely to involve modification of the T lymphocyte response to subsequent allergen exposure with a shift in the Th2/Th1 T lymphocyte balance, either by immune deviation Th2/Th1 responses (4) or down-regulation of Th0/Th2 responses possibly as a consequence of induction of T-cell unresponsiveness (anergy) (4,5).

We have recently completed 2 further controlled clinical trials in patients with severe summer hayfever. In the first, we examined the effects of high dose conventional subcutaneous immunotherapy (*Phleum pratense*, Alutard SQ) in patients with hayfever and seasonal asthma with increases in bronchial hyperresponsiveness. In this study, in which each subject acted as his/her own control, we identified a 50% reduction in symptoms, an 80% reduction in rescue medication and a 2-3 doubling doses reduction in airway responsiveness to methacholine (increase in methacholine PC20) during the pollen season. Clinical improvement was accompanied by a marked improvement of quality of life in 5 out of 7 domains, suppression of early and late skin responses and a 30-40 fold increase in allergen-specific IgG4 concentrations. We used a rapid up-dosing "cluster" immunotherapy protocol in 7 visits over 3½ weeks with antihistamine pre-treatment. No large local and no systemic reactions were observed in either group.

In a separate study, we investigated 57 patients with moderate/severe hayfever due to grass pollen allergy in a double-blind, placebo-controlled trial of high dose sublingual grass pollen immunotherapy

(*Phleum pratense*, aqueous extract in glycerol, ALK-Abelló, Denmark). Patients were up-dosed with 3 times weekly sublingual drops for 6 weeks, followed by daily sublingual drops for 18 months, with a total administered monthly dose 30 fold higher than the conventional subcutaneous dose. Although there was no significant improvement in primary outcome measures (symptoms and rescue medication) there was a significant improvement in the patients' overall assessments ($p < 0.01$), which correlated with a significant reduction in the late skin response ($p < 0.003$, $r = -0.47$, $p < 0.05$) and an increase in allergen-specific IgG4 ($p < 0.01$). These results indicate the need for a large multicentre dose-ranging study for sublingual immunotherapy (6,7).

In summary, allergen immunotherapy is particularly effective in patients with seasonal pollenosis, it reduces seasonal asthma and bronchial responsiveness and improves quality of life. Long-term benefits following discontinuation, as confirmed by several groups, indicate that immunotherapy is the only treatment with the potential to modify the course of the disease. The sublingual route may represent an alternative route, which is safer, although likely to be less efficacious than the subcutaneous route, which remains the gold standard.

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Preventive allergy treatment through specific allergy vaccination



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Background

Specific allergy vaccination, allergen specific immunotherapy (SIT), is the only treatment that interferes with the basic pathophysiological mechanisms of the allergic disease. Allergen avoidance is always the first-line treatment and, although not completely effective, it may reduce the need for further intervention. Drug treatment is often the next logical step to reduce disease severity, but in patients with a constant need for pharmacotherapy, the advantages of instituting SIT early in the evolution of the disease, e.g. while severity of the disease is still modest and at a time when the possibility to prevent deterioration into asthma is highest, should be seriously considered. Immunotherapy can significantly reduce the severity of the allergic disease and the need for anti-allergic drugs, consequently improving the quality of life for allergic patients.

Key message

A significant proportion of rhinitis patients has minimal persistent inflammation during allergen exposure in the lower airways. This inflammation is often under-diagnosed and therefore inadequately treated. SIT might, as the only treatment, improve inflammation independently of the shock organ. Allergen induced IgE-mediated inflammation should therefore be seen as a multi-organ disease, and SIT should be based on the allergen sensitisation rather than on the specific disease.

Summary

From a clinical point of view, it is clear that there is a link between allergic rhinitis and asthma. Up to 38% of the rhinitis patients report seasonal lung symptoms and more than 70% of the asthma patients report nasal symptoms. About 20% of all allergic rhinitis patients develop asthma later on in life. It has been found that 11-73% of allergic rhinitis patients shows bronchial hyperresponsiveness outside the pollen season and up to 50% during the season. Rhinitis frequently precedes the onset of asthma, and patients with allergic rhinitis who also have bronchial hyperresponsiveness are more likely to develop asthma. When SIT is introduced to patients with only allergic rhinitis, SIT may stop the development of asthma. The early study by Jonhstone and Dutton with several different

allergens showed that 28% of the children receiving specific immunotherapy developed asthma as compared to 78% placebo-treated children. The European multi-centre Preventive Allergy Treatment (PAT) study in children aged from 7 to 13 supports the hypothesis that in children with seasonal rhinoconjunctivitis, SIT has a preventive effect on later development of asthma. In a study in tree pollen allergic adults suffering from allergic rhinitis, it was found that none of the patients initially suffering only from allergic rhinitis developed asthma during the total study period of 8 years.

To determine whether SIT could prevent the development of new sensitisations over a 3-year follow-up survey, a prospective, non-randomised study was carried out in a population of asthmatic children under 6 years, whose only allergic sensitivity was to house dust mites. In this study, 22 children who were receiving SIT were compared with 22 other children age-matched and monosensitised to house dust mites. Around 45% of the children receiving SIT did not develop new sensitivities vs. none in the control group. This study suggests that SIT with house dust mite extract alters the natural course of allergy in preventing the development of new sensitisations.

Conclusion

Specific allergy treatment in the form of SIT performed with a characterised and standardised allergen extract in an optimal dosage is so far the only treatment for allergic diseases that has been shown to interfere with the basic mechanisms of the allergy.

Antihistamine treatments combined with specific allergy vaccination



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When performing specific allergy vaccination, a balance between increasing clinical efficacy and restraining possible side effects is essential. Due to the use of standardised allergens, clinical efficacy could be raised in the last decades leading to an average reduction of clinical symptoms by 70 to 80 percent. Although these results must be quoted as good, attempts to reach an even better outcome must be achieved.

Severe systemic side effects have limited the application of specific allergy vaccination in reaching a broad population. In Great Britain restrictions by the government have almost stopped specific allergy vaccination.

Improvement in the safety of application of specific allergy vaccination changed the restricted opinion, so that nowadays most patients and doctors favour specific allergy vaccination in allergic patients. Besides improved quality of specific allergy vaccination, the antihistamine pre-treatment, as has been proposed by us for the first time in 1988, has convinced many doctors to use this kind of regimen. In the meanwhile many double-blind studies have proved the concept of antihistamine pre-treatment, which is able to reduce local reactions as well as parts of systemic reactions.

In addition to that, a recent publication by Müller and co-workers demonstrates that antihistamine pre-treatment does not only reduce side effects, but also seems to improve the clinical outcome of specific allergy vaccination. In their study of insect allergic patients, none of the rechallenged patients having had antihistamine pre-treatment experienced a systemic reaction in contrast to those having received just immunotherapy with placebo ($p < 0,01$).

Antihistamine pre-treatment does not only improve the safety of specific allergy vaccination, it also seems that clinical improvement can be ameliorated.

Corticosteroid treatments combined with specific allergy vaccination



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There is a documented effect of treatment with topical nasal steroids and specific allergy vaccination (AV) on clinical symptoms and related cellular changes in allergic rhinitis. Studies have also shown beneficial effect of both treatments on bronchial hyperresponsiveness alone or as a feature of allergic asthma. Allergy vaccination being a systemic treatment is expected to have a general effect on the expression of allergic disease in all affected organs. The mechanism behind the effect of nasal steroids on bronchial symptoms and hyperresponsiveness is still a matter of discussion. Very few studies attempted to compare anti-inflammatory treatment of both therapies in the same group of patients. In patients with rhinitis, Juniper compared preseasonal allergy vaccination with nasal beclomethasone, and in an open non-randomised study on asthmatics, Shaikh compared inhaled steroid treatment with AV, both studies were inconclusive.

We have performed a comparative study of allergy vaccination and topical nasal steroid treatments in our model of seasonal allergic disease where both upper and lower airway symptoms and medication were examined. We investigated 41 birch pollen allergic patients with rhinoconjunctivitis and asthma in a randomised, double-blind, comparative study with birch AV and Budesonide Turbuhaler 400µg. Based on the severity of the disease (analogue scale) during preceding seasons, symptoms (upper and/or lower airways) and PC20 values of the preseasonal methacholine test, the patients were allocated to two groups, one with rhinoconjunctivitis only and the other with rhinoconjunctivitis and asthma. Within each group, the patients were randomised to two different treatment methods and/or their placebo. AV was initiated preseasonally, and all patients reached maintenance dose before the start of the season. Treatment with nasal steroid was started 10 days before birch pollination. Symptoms from rhinoconjunctivitis increased significantly in both groups during the season, but significantly less in the steroid-treated group at the end of the season. PEF values in the season decreased significantly in the topical steroid-treated group, but not in the AV-treated group. The use of medication for both rhinoconjunctivitis and asthma were not significantly different between the groups. In the rhinitis group, a significant seasonal increase

of PC20 values was found, while in asthmatics only in the steroid-treated group increased BHR was observed. AV treatment prevented effectively PC20 changes in asthmatics in agreement with our earlier results.

In conclusion, following a short course of preseasonal AV the effects on symptoms of rhinoconjunctivitis were comparable in both treatment groups at the beginning of the season and better in the nasal steroid-treated group at the end of the season. In asthmatic patients, the AV-treatment had clearly beneficial effect as measured by PEF, PC20 and *in vitro* parameters compared to nasal steroids. Because of extreme atmospheric conditions and pollen count, an increase of BHR was noted in most of otherwise rhinitic patients. The systemic character of the treatment explains the positive effect of AV on asthma symptoms, while the local effect on rhinitis is more pronounced in the nasal steroid-treated group. Another important clinical outcome, need for rescue medication, demonstrated equal use of drugs in both treatment groups. Further increase in effectiveness of AV is expected after a longer period of treatment.

Anti-IgE treatment combined with specific allergy vaccination



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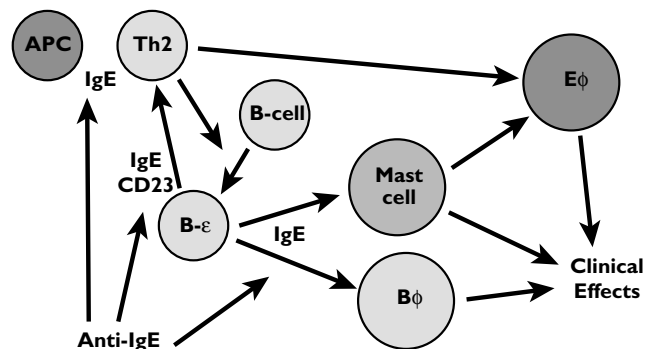
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The development of non-anaphylactic monoclonal antibodies directed against IgE (anti-IgE) has given us a very useful tool for exploring the relevance of IgE in a variety of clinical settings. Anti-IgE reduces the serum concentration of free IgE, attenuates responses to inhaled allergens and allows reductions in steroid doses in patients with asthma.

In addition, several research groups have expressed interest in using anti-IgE as an adjuvant to improve the safety and efficacy of specific immunotherapy. There are three distinct ways that anti-IgE could help: As a prophylactic agent to increase safety in the induction phase; as an add-on during the pollen season to increase the effect of SIT; as an adjuvant - modifying antigen presentation during immunotherapy.

Preliminary data presented by Wahn et al. (EAACI Berlin, May 2001) suggests that administration of anti-IgE during the pollen season may have a synergistic effect with SIT. No data have been published on the use of anti-IgE prior to or during SIT, but there are *in vitro* data supporting this strategy. As well as reducing the number of IgE molecules available to bind to effector cells, anti-IgE decreases the expression of high and low affinity IgE receptors and the expression of L-selectin. This will interfere with antigen presentation, by excluding B-cells from acting as APC for IgE-Ag complexes and suppressing FcεRI-mediated activation by dendritic cells of Ag-specific Th2-cells at low concentrations of antigen. Moreover, any circulating IgE-Ag complexes will become coated by anti-IgE, and the resultant complex will be taken up into APCs via the IgG Fc tail of anti-IgE. This should focus antigen to APC bearing FcγR instead of FcεRI and should hence promote induction of Ag-specific IgG rather than Ag-specific IgE.

Immunological actions of anti-IgE



Cytokines and anti-cytokines for treatment combined with specific allergy vaccination



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Regardless of its weak or strong symptom-related biological efficacy in animal systems, a treatment based on allergens combined with (anti)-cytokines will allow new insights and a better understanding of specific allergy vaccination and its underlying mechanisms. In how far a strategy combining allergens *and* (anti)-cytokines might be an option for the treatment of allergic disorders in humans remains to be elucidated.

An interesting strategy to increase immunomodulatory and clinical effects of specific allergy vaccination (specific immunotherapy with allergens) might be a combined treatment with cytokines or anti-cytokine compounds and relevant allergens. Since successful allergy vaccination has been demonstrated to promote a T-helper (Th)1-like response, interleukin (IL)-12, IL-18 or INF- γ represent candidates for a beneficial shift away from Th2-driven allergic disorders. An antagonising Th2-like response by anti-IL-4 or anti-IL-13 or soluble receptors of these IgE-inducing cytokines appears to be another option altering the allergic immune response. Promoting T-cell tolerance by IL-10 might be an additional route to enhance the effects of specific allergy vaccination.

So far, allergen specific treatment with the addition of (anti)-cytokines has been exclusively applied in mouse models of immediate type hypersensitivity or allergy-like disorders. IL-12 and IL-18 applied as fusion proteins with specific allergens have indeed demonstrated to redirect allergy-promoting Th2- to a Th1-type response with changes in cytokine and immunoglobulin production and a decrease in organ specific hypersensitivity. Liposome encapsulated IL-12 via oral route has been beneficial, abolishing the development of an anaphylactic hypersensitivity during sensitisation with biologically relevant allergens (i.e. peanut). There is increasing evidence that adjuvants from microbial origin (i.e. immunostimulatory DNA sequences) have a strong impact on cytokine production and subsequent (allergic) immune responses. A number of studies have clearly demonstrated that this approach might promote a more complex, but co-ordinated change in the network of inert and antigen specific immunity with their molecular and cellular players. In contrast, application of specific allergens with a single (anti)-cytokine might create more subtle and presumably more limited effects. Another issue is related to the optimal application of (anti)-cytokines combined with allergy vaccination. Based on their localised effects, allergy-related cytokines should target immunologically active sites interfering with the allergen specific immune response driven by antigenpresenting cells, T- and B-lymphocytes.

Molecular engineering of allergens for therapy.

Theoretical considerations



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By definition, a vaccine changes the immune system in such a way that it results in protection. Allergy vaccines are unusual (but not exceptional) for two reasons. 1) The immune response needs to be changed, rather than induced or enhanced and 2) the inoculum itself is harmless, but the interaction of the inoculum with the immune system is potentially dangerous. The main purpose of molecular engineering of allergens is to broaden the therapeutic window that is set by safety and efficacy considerations. Both safety and efficacy may, at least in theory, be influenced favourably by the inclusion of an “adjuvant”, either as separate component of the vaccine formulation or as a component linked to the allergen-related substance.

Safety requires a preparation that 1) will not easily trigger sensitised mast cells, 2) will not unduly enhance the production of pre-existing IgE antibodies and 3) will not result in the production of significant numbers of new IgE specificities. An obvious approach is the reduction of the number of IgE-reactive epitopes per allergen (either by deletion of epitopes or by a substantial reduction of the affinity for IgE antibodies). The crucial (and as yet unsolved) question is how this affects efficacy.

Another aspect of the safety of allergen vaccine preparations is not unique for allergy: The presence of potentially harmful contaminants, either toxic or infectious. Particularly in relation to vaccines derived from mammalian sources, viruses and prions are of major concern. This is a strong argument in favour of recombinant allergens.

Discussion of optimal efficacy obviously requires an understanding of the working mechanism(s) and the target cells for the treatment. These are likely to be different for different types of allergen-specific immunotherapy (e.g. venom rush therapy, sublingual therapy or “classical” therapy). Some effects may work via mast cells, but effects on B-cells and/or T-cells are likely to be most relevant, whereas pre-existing IgE-producing plasma cells are unlikely to be affected by any of the current treatment protocols.

Down-regulation of “bad” T-cells, up-regulation of anti-inflammatory T-cells and/or the induction of

blocking (allergen-inactivating) antibodies (IgG4?) are assumed to be involved. Originally, allergen-inactivating antibody was supposed to block the allergen mast cell interaction. More recently another target for blocking antibody has received attention: Blockage of allergen-induced activation of pro-inflammatory T-cells via interference with antigen presentation.

In contrast to T-cells, B-cells need a properly folded protein to produce antibodies that are able to inactivate the allergen. If, as still seems likely, blocking antibodies are relevant for efficacy, the allergen vaccines of the future will contain near-native allergen structures mixed with, conjugated to, or grafted into effect-modifying adjuvant structures.

Mutated major allergens for vaccination



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Specific Allergy Vaccination, i.e. specific immunotherapy, is a causal treatment with curative potential in selected patients with allergic diseases, such as hay fever and asthma. Optimal dosing, however, is limited by the risk of inducing systemic allergic reactions caused by the allergens. Safe vaccines for specific allergy vaccination would facilitate the use of the treatment, not only by specialists, but also in general practises for the benefit of allergic patients.

Several molecular strategies have been applied to reduce the allergenicity of allergy vaccines. Some approaches aim at eliminating IgE binding and address only allergen specific T-cells, which play an important role in the regulation of the allergic immune response. This has been achieved by chemical modification or by disrupting the overall tertiary folding pattern of the allergen molecule by using synthetic peptides, mixtures of truncated molecules or by targeting cysteine residues engaged in disulphide bonding by site directed mutagenesis.

Other approaches aim at reducing allergenicity while conserving immunogenicity, i.e. the capacity to induce protective immune responses, thus targeting both allergen specific B- and T-cells. Epitope engineering has been applied to substitute solvent exposed amino acid residues located in major IgE binding epitopes, or segments of genes encoding homologous allergens has been shuffled to yield hybrid molecules with reduced allergenicity.

Pre-clinical results from our laboratory based on the last two strategies indicate, that recombinant allergen variants are promising active ingredients in novel allergy vaccines with both high safety and efficacy profiles.

Vaccination with peptides



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A major obstacle to widespread uptake of specific immunotherapy (SIT) is the occurrence of IgE-mediated adverse events. Such events represent a significant risk to the patient and also limit the dose of allergen administered. The result is a lengthy, resource intensive treatment, which may last several years.

The use of short peptide sequences corresponding to T-cell epitopes may circumvent the limitations of conventional SIT by targeting allergen-specific T-cells in the absence of IgE crosslinking on the surface of mast cells and basophils. In order to investigate the role of the T-cell in allergic asthma, we administered peptides from the major cat allergen Fel d 1 to cat allergic asthmatic subjects via the intradermal route. Some individuals developed isolated late asthmatic reactions (LAR) that were MHC-restricted and IgE-independent. Subsequent rechallenge with the same dose demonstrated the induction of peptide- and whole allergen-specific T-cell hyporesponsiveness (Haselden et al., *J. Exp. Med* 1999; 189:1885).

Subsequently we have demonstrated the dose-dependency of isolated LAR and the ability of a single dose of peptides to induce long-lasting hyporesponsiveness and reduction in the cutaneous late-phase reaction to intradermal challenge with whole cat dander (Oldfield et al., *Jl* 2001; 167: 1734).

More recently, we have performed a randomised, double-blind, placebo-controlled study of peptide immunotherapy using a prototype Fel d 1 peptide vaccine containing a mixture of 12 peptides spanning the majority of the allergen. A total dose of 90 µg was administered over a minimum of 2 weeks. The study was powered on cutaneous late-phase reaction data from the previous study (Oldfield et al.). Reduction in the late cutaneous reaction to whole allergen was the primary outcome measure. Responses to cutaneous and inhaled challenge with whole allergen were performed before and after peptide therapy. The treatment resulted in a significant reduction in the magnitude of both the early-phase and late-phase reaction to intradermal challenge with whole allergen. A quality of life questionnaire relating to exposure to cats

demonstrated a significant improvement in symptoms in the active treatment group and no change in the placebo group.

In a separate, open study, peptides were administered at 2 weekly intervals starting at a dose of 0.1 µg rising gradually to a final injection of 25 µg. No isolated LAR were recorded in this study, but a marked reduction in the cutaneous late-phase response to intradermal challenge with whole cat dander allergen extract was demonstrated. The results indicate that optimised dosing and dose interval will allow the safe and efficacious introduction of peptide-based immunotherapy without the induction of IgE-mediated adverse events or isolated LAR. Furthermore, the ability to deliver high doses of standardised, highly pure peptides will result in substantially reduced treatment periods.

CpG motive vaccines as adjuvants



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Special immunostimulatory DNA sequences have been shown to act as strong Th1 response-inducing factors. This effect is mainly due to unmethylated CG dinucleotides in certain sequence contexts. These "CpG-motifs" are frequent in bacterial DNA, but underrepresented in vertebrate DNA. The potent immunologic response to oligonucleotides (ODN) containing CpG-motifs suggests that bacterial DNA serve as an evolutionary conserved ligand for the vertebrate immune system, which recognises this structural pattern as danger-signal. The mechanisms through which CpG-motifs exert their effects have not been revealed in detail yet.

One strategy to improve the efficacy of specific immunotherapy (SIT) is to administer the allergen-vaccine together with special adjuvants, which can induce and/or amplify the expected immunologic effects. Atopic allergies can be classified as Th2-diseases. Consequently, adjuvants creating a Th1-milieu at the site of the immunological reaction could help deviating the atopic immune response. Data from the literature indicated that ODN containing two or three CpG-motifs induced the production of Th1-cytokines (Interferons, IL-12) in NK-cells and antigen-presenting cells. This led to a suppression of IgE-production while allergen-specific IgG- and IgM-production *in vitro* increased. Moreover, the administration of allergen together with - or coupled to - allergens induced typical Th1-responses in animal models. Though the doses applied in these studies did not lead to any obvious vital complications in the test animals, the potential of toxicity is of concern. In particular, excessive inflammatory reactions of the Th1-type may occur, another matter of concern would be the activation of auto reactive (DNA-reactive) immune cells. Current research evaluates the risk connected with the use of CpG-containing DNA as adjuvants in humans. Only *in vivo* studies will answer the question whether these adjuvants can be used to improve allergy vaccines in the future.

DNA vaccines



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Plasmid DNA (pDNA) encoding an antigen or allergen and injected i.m. or i.d. is taken up by somatic cells and antigen presenting cells. These cells produce the antigen resulting in a predominant Th1 immune response. Since only small amounts of antigen or allergen are secreted by such transfected cells, it is highly unlikely that this type of immunisation would cause allergic and certainly not anaphylactic adverse reactions. Therefore, we reasoned that allergen gene immunisation could offer a novel and safe form of allergen immunotherapy. However, preliminary pDNA immunisations in mice with a pDNA construct containing the short ragweed allergen Amb a 1 gene yielded only very weak immune responses. The reason for this may have been an inefficient transcription of this allergen gene, since it is not a mammalian gene. Therefore, we investigated whether we could enhance the pDNA induced immune response to Amb a 1 by modifying the Amb a 1 gene for a more efficient transcription by mammalian cells. Furthermore, we determined whether the pDNA induced immune response could be enhanced by co-injection of an immunostimulatory CpG-motif oligodeoxynucleotide (ISS-ODN) as an adjuvant.

First, we removed the plant signal sequence of the Amb a 1 gene and replaced it with the influenza hemagglutinin signal sequence. This resulted in a 3-fold increase of Amb a 1 secretion by *in vitro* transfected 3T3 cells and an 8-fold increase in the IgG2a anti-Amb a 1 titer in BALB/c mice. We then “humanised” the Amb a 1 gene by replacing the codons typically used by plants but not mammals for certain amino acids with their human counterparts. This resulted in a 10-fold increase in Amb a 1 secretion by 3T3-transfected cells and a 65-fold increase in the IgG2a titer in mice. Since the IgG2a titer was still relatively low, we injected the modified and humanised Amb a 1 gene pDNA construct together with an ISS-ODN adjuvant. At the optimal concentration of the ISS-ODN, the IgG2a titer further increased and was 750-fold greater than that obtained by the original immunisation with pDNA containing the unmodified plant Amb a 1 gene and no adjuvant.

This modified Amb a 1 gene pDNA/adjuvant vaccination was then used to “treat” mice that had been pre-immunised with Amb a 1 in alum and had high IgE anti-Amb a 1 titers. By treating the mice with 3 biweekly injections, the IgE titer was reduced by 90% in 6 weeks compared to that of control mice injected with saline or empty vector. Mice injected with modified Amb a 1 gene pDNA or co-injected with this pDNA and a non-ISS ODN had a 40% reduction of the IgE titer. Mice injected with ISS-ODN alone had a 24% reduction of the IgE titer.

In conclusion, the data show that for obtaining potent allergen gene pDNA vaccination, the allergen gene has to be modified to be efficiently transcribed by mammalian cells and the pDNA injected together with an adjuvant.

Mycobacterium vaccines as adjuvants



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Background

Mycobacteria, of which there are more than 80 species in soil and water, are ubiquitous in the environment and could, thus, influence significantly the programming of the immune system by promoting Th1-type cytokine responses. Exposure to mycobacteria in childhood, at a time when Th2-type T-cell responses prevail, could stimulate Th1 cytokine generation and thus help establish a balance between Th1 and Th2 cytokines. The epidemiological evidence for the effects of mycobacteria on the development of allergic diseases is controversial, with one study showing a protective effect and another no effect.

Key message

Accumulating evidence from epidemiological studies, *in vitro* studies with human blood cells, *in vivo* studies using animal models and early clinical trials suggest that *Mycobacteria*, especially the nonpathogenic species *M. vaccae*, may modulate the way the immune system responds to common allergens.

Summary

M. vaccae prevents sensitisation or alters responses after sensitisation to ovalbumin and generation of Th2-type cytokines, as shown by reduced serum IgE and IL-5 synthesis by spleen cells taken from sensitised mice. The inhibitory effect takes time (about 3 weeks) to develop and results in a significant reduction in eosinophil numbers in bronchoalveolar lavage fluid, blood and bone marrow. Pre-treatment also inhibits the development of bronchial hyperresponsiveness to methacholine. Importantly, the inhibitory effect is sustained, being present as long as 9 weeks after injection.

The first study to employ *M. vaccae* to alter allergic disease in humans has been that by Hopkin and colleagues. In a double blind, placebo-controlled study, these authors showed that treatment with vaccine caused on average 70% fewer symptoms and 90% less bronchodilator use. The second study, which further added to the concept of protective effects of *M. vaccae*, has been that of Camporota et al. A single intradermal injection of *M. vaccae* (SRL-172) was able to significantly ($p=0.005$) attenuate the late phase asthmatic response (LAR) by an average of 30% when given 3 weeks prior to

allergen challenge. In the same study, there was a tendency ($p=0.07$) towards reduced allergen-stimulated production of IL-5 by PBMC in vaccinated subjects, with a similar effect being seen when measuring serum IgE levels.

Finally, a recent unpublished study by Arkwright et al. in children suffering from atopic dermatitis has shown a dramatic reduction in the extent of eczematous changes in children treated with a single intradermally administered dose of SRL-172.

Conclusion

Studies in animals show clear efficacy of at least two strains of mycobacteria at reducing sensitisation to ovalbumin. This appears to be linked to increased Th1 cytokine production in response to the mycobacterium and generation of regulatory T-cells, with concomitant reduction in Th2 cytokines. Whilst this evidence is encouraging, the implications for human disease are unclear. Apparent differences between protective effects of BCG in two different populations raise interesting questions about genetic influences as well as influences of natural exposure to mycobacteria. Furthermore, the route of entry of mycobacteria may be equally important. As yet there are no studies that have examined the effects of oral administration, but clearly these need to be done.

Are both B- and T-cell allergen epitopes required for optimal effect of specific allergy vaccination?



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Vaccination with T-cell epitopes is sufficient to mediate allergen immunotherapy

In order to avoid the potential risk of inducing anaphylaxis that may accompany the use of native allergen, the development of candidate vaccines based on chemically modified allergens, mutant recombinant allergens and allergen derived peptides has attracted attention. They are designed to have reduced IgE binding but retain the capacity to stimulate allergen specific T-cells. The experiments reported here investigate if immunisation with an immunodominant T-cell epitope is sufficient to inhibit pathogenic responses in a murine model of Der p 1 induced allergic inflammation.

The immunodominant T-cell epitope of Der p 1 for the high responder (H-2^b) mice is located within residues 110-130 (p 1, 110-130). The peptide was delivered either in soluble form intranasally or systemically targeted to scavenger receptors (SRs) expressed on antigen presenting cells (APCs). The intranasal administration of p 1, 110-130 resulted in peripheral tolerance and reduced pulmonary eosinophilia, which was mediated by regulatory T-(Tr) cells, characterised by their cell surface phenotype (CD4⁺, CD25⁺, CD45RB^{low} and CTLA-4⁺). The induction of these Tr-cells required co-ordinated production of IL-10 and Notch signalling in conjunction with TCR ligation. Systemic delivery of p 1, 110-130 targeted to SRs also inhibited pulmonary eosinophilia by promoting the synthesis of Th1 cytokines. Immunisation of naive mice with SR targeted p 1, 110-130 induced Der p 1 specific Th1 immunity, characterised by the production of high levels of IFN- γ , which prevented the development of allergic inflammation. Vaccinating mice that had established Der p 1 specific Th2 responses with SR targeted peptide also increased IFN- γ production. In parallel, IL-5 synthesis was reduced, IL-10 levels remained unchanged and ratio of IgE/IgG2a was altered in favour of Der p 1 specific Th1 immunity.

In conclusion, vaccination with peptide containing an immunodominant T-cell epitope can reduce allergic inflammation through either the induction of Tr-cells that mediate peripheral tolerance or by promoting Th1 cytokine production.

Are both B- and T-cell allergen epitopes required for optimal effect of specific allergy vaccination?



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The role of B- and T-cell epitope recognition in immunotherapy

Excessive IgE antibody production is the cause of immediate type allergic reactions. In contrast, specific IgG, in particular IgG₄, reflects normal immunity to soluble antigens. Synthesis of both IgE and IgG₄ antibodies by B lymphocytes is controlled by specific T lymphocytes secreting distinct cytokine patterns upon activation. The quantitative and qualitative cytokine composition results from specific activation by antigenic peptides, which are processed by antigen presenting cells (APC) and presented in the context of MHC-II to specific T-cells. The cytokine response is strongly influenced by type of APC engaged. APC that utilise phagocytosis or pinocytosis for antigen uptake, such as monocytes, macrophages and dendritic cells, internalise allergen molecules independently of their structural features. On the other hand, IgE bearing B-cells generated in the memory response and IgE bound to CD23 on B-cells can focus and specifically present allergen to the T-cells at about 100 times higher efficiency than other types of APCs. Accordingly, IgE also acts as an Ig specialised in antigen capture and focusing and presentation. Therefore, the presentation of low doses of allergen to lymphocytes is greatly enhanced by B-cell and IgE-facilitated antigen presentation. B-cells that are utilised to present antigen to the CD4⁺ T-cells at extremely low concentrations elicit an IL-4 dominated cytokine profile with very little IFN- γ and increased memory IgE synthesis. In contrast, the usage of monocytes and macrophages and high antigen doses results in high IFN- γ but low IL-4 synthesis. Furthermore, allergen-crosslinking of specific IgE on mast cells and basophils degranulates these effector cells of allergy and mediates allergic reaction. Accordingly, IgE not only elicits an allergic reaction, it is also important in the development of the secondary IgE response.

Whereas IgE antibodies almost exclusively recognise three-dimensional structures exposed at the allergen surface, T-cells in the context of MHC-II recognise short antigenic peptides. The intact T-cell epitope peptides however, are essential in regulatory T-cell activation and specific tolerance induction. Tolerance to allergens is a typical feature of normal

immunity and induction of peripheral T-cell tolerance is a key step in specific immunotherapy (SIT). Indeed, minimal size T-cell epitope peptides alone are sufficient for allergen-specific tolerance induction and successful SIT. Therefore, structural variants of allergens, which specifically target T-cells in specific tolerance induction, but lack specific IgE antibody-binding sites, are candidates for safe immunotherapy without risk of anaphylaxis and further IgE facilitated responses.

Tolerance to allergens in both normal immunity and SIT is induced by IL-10 and TGF- β . Whereas IL-10 alone is produced in normal response and SIT to insect venoms and is responsible for specific tolerance induction, IL-10 and TGF- β both contribute in development and maintenance of mucosal tolerance. This was shown by neutralisation of specific cytokine activity. In addition, IL-10 promotes IgG₄ production and suppresses IgE, whereas TGF- β induces IgA switch and synthesis. The state of peripheral tolerance to house dust mite and birch pollen was fully established in SIT by these two cytokines after 28 days. Further experiments demonstrated that both cytokines elicited specific T-cell suppression by inhibiting the CD28 costimulatory pathway. Together, these data demonstrate that specific tolerance induction in peripheral T-cells is a crucial step in SIT to inhaled allergens and that normal immune responses to mucosal allergens are under the control of IL-10 and TGF- β .

Are both B- and T-cell allergen epitopes required for optimal effect of specific allergy vaccination?



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Specific Immuno Therapy (SIT) is a highly effective mode of immuno-intervention. It is well established that SIT affects both T- and B-cell responses in an allergen-specific manner. Regarding the modulation of the T-cell responses, several mechanisms are being proposed: The induction of regulatory T-cells, induction of Th-1 immune responses, suppression of Th-2 cells or stimulation of CD8 responses. Although the detailed immunological mechanisms have not been completely worked out, it is clear that the allergen needs to be presented to the T-cells by antigen presenting cells. Therefore, the allergen must be provided in such a form that T-cell epitopes are efficiently cut out of the entire allergen.

In addition, modulation of B-cell responses has also been described. They include the concept of "blocking antibodies". B-cell responses can be effected in several ways: Either via T-cells (see above) or directly by interaction of the allergen with the B-cell antigen receptor (surface immunoglobulin). The latter mode of interaction requires the presence of B-cell epitopes. However, it is still not completely elucidated to which degree this mode of allergen B-cell interaction contributes to the success of SIT.

It needs to be emphasised that the presence of intact B-cell epitopes always leaves the risk of the induction of anaphylactic reactions. Therefore, if it turns out that B-cell epitopes are indeed required for optimising SIT, a strategy needs to be developed to avoid such reactions.

The classical specific allergy vaccination. Recommended administration procedures



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The clinical advantages of injection allergen-specific immunotherapy are contra-balanced by a potential risk of inducing systemic side effects. Although the frequency of serious systemic reactions is low, the treatment principle of injecting allergen extracts into IgE-sensitised patients always implies a risk of inducing anaphylactic reactions. An essential point in discussing risk assessment is to use a clinically meaningful and internationally accepted grading system for systemic reactions. It is of fundamental importance in minimising the risk of systemic side effects to identify risk patients and factors, to institute procedures to monitor patients before injections and to adjust dosages in accordance with defined rules.

Risk factors are related to the disease treated and to the allergen extracts and the induction schedule applied. Asthma, especially uncontrolled asthma, is a significant risk factor for the induction of systemic reactions. Hymenoptera venom allergic patients do not seem to be at great risk, but when these patients do react to allergen injections, it is often with severe systemic symptoms. Dose escalation in relation to increased allergen exposure, i.e. during pollen seasons increase the risk of inducing side effects. It is recommended to use standardised extracts with a documented potency and consistency between production batches in order to prevent overdosing when changing to a new vial. The aggressiveness of the induction regimen is a balance between the risk of inducing systemic reactions and the time consumption for reaching the maintenance dose. Single injections once a week for the induction treatment is generally a safe and well tolerated regimen, in contrast to rush immunotherapy that may imply an increased frequency of side effects. A clustered induction regimen (2-4 injections per visit) represents a compromise of a patient-friendly fast regimen not showing an unacceptable high frequency of systemic reactions.

Procedures to minimise the risk and to improve the safety of allergen injections are related to the human factor, the pre-injection monitoring of the patient's suitability to receive injections, and the recognition and immediate treatment of systemic reactions. A major issue is to alleviate as much as possible the human factor in terms of mistaking patients, allergen

extracts and dosages. Important is likewise a methodical monitoring of every patient before the injection in terms of conditions that may enhance the risk, e.g. recent airway infections, recent exposure to allergens or increased needs for anti-allergic treatment, prolonged intervals between the injections, and systemic reactions to the preceding treatment. The cornerstone in reducing side effects is based on education and training of the staff in the process of deciding the dose and dosage modifications. Involving the patient actively in the safety monitoring might be helpful and improves patient compliance by making the patient an active partner in the treatment. Finally, if anaphylactic reactions are induced, a successful outcome is related to the staff being able to identify the early signs and to institute immediate rescue treatment.

Venom specific allergy vaccination. Recommended administration procedures



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Since whole body extracts were substituted by purified venom extracts in the 70s, specific allergen vaccination (SAV) for insect sting allergy has been one of the most established areas for this kind of treatment. It has been possible to perform SAV with much more rapid schemes than in patients with inhalation allergy. This is probably due to the fact that patients allergic to insect venom have had and will have a short and well-defined exposure when stung, in contrast to inhalant allergy which often has a long season of exposure, perennial if cross-reacting food allergens are taken into account, and often unrecognised (animals and mites). In addition, patients with inhalation allergy often present reactions to irritant substances, and aggressive SAV in such (almost) symptomatic patients will be difficult.

Ultra rush treatment has become popular. By this treatment maintenance dose is reached within few hours with a limited number of injections, if no severe side effects occur. The treatment has to be performed in an intensive ward to allow proper monitoring and treatment.

Rush treatment is less well standardised. Generally maintenance dose is reached within a few days. In a modified version, **clustered SAV**, series of injections are administered at weekly intervals.

Traditional/conventional SAV involves weekly injections. It takes several months to reach maintenance dose (and protection to future stings). Depot extracts are often administered according to such schedule. In a multi-centre study, traditional schedules had less side effects than rush regimens, but ultra rush was not analysed separately. In other studies, the ultra rush modality had very few side effects.

Antihistamine pre-treatment was feared to mask mild side effects and thereby permitting “overdosing” and subsequent severe side effects. This has not been the case; on the contrary, less severe local and systemic side effects occur in pre-treated patients.

The **duration of SAV** and **when to stop** have been intensely discussed. Unfortunately, no *in vitro* tests can predict the degree of protection with certainty.

Even an uneventful sting challenge cannot guarantee a subsequent full protection. At present, treatment for 5 years is generally recommended. In patients with increased risk (bee allergic patients, patients with many side effects during treatment, patients with very severe sting reactions etc.), a longer treatment period can be considered.

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Sublingual immunotherapy and other mucosal routes



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The sublingual/swallow (SLIT) route for specific vaccination is, at present, considered a viable alternative to the injection route (1-2). This opinion, expressed in the official documents, was indeed based on few DBPC studies. During the last two years, many randomised trials were published. At present, there are eighteen controlled trials, most of them providing experimental proofs of SLIT's efficacy in the treatment of allergic rhinitis. Moreover SLIT was also demonstrated capable of reducing asthma symptoms (3-5), the use of rescue medications and of improving the quality of life (3).

The demonstration of the clinical efficacy prompted scientists to investigate the possible mechanisms of action of sublingual route. SLIT was shown able to downregulate the inflammatory phenomena directly in the target organs (6-7), but also an effect on T-cell proliferation in response to allergens was demonstrated in *in vitro* models (8-9).

Due to its good safety profile, SLIT seems particularly suitable for paediatric patients, therefore the WHO position paper recommended further studies in children. During the last two years, several paediatric trials (10-12) and post-marketing studies (13-14) appeared, and confirmed the favourable safety profile of SLIT. Thus the more recent WHO position paper proposed the use of SLIT also in this age range (15).

Concerning the comparison to injection immunotherapy, we have two studies available. The first (16) is an open one showing a better efficacy of injection IT with dust mites especially on asthma symptoms. The second one (17), conducted in a double blind, double dummy fashion, showed that injection immunotherapy and SLIT have superimposable efficacy.

Some interesting pharmacokinetics data have been provided in humans for local routes showing, for instance, the long-lasting persistence of the allergen on the mucosae, the absence of bronchial deposition and the absence of direct sublingual absorption (18). These facts were confirmed also using a commercial preparation administered to allergic volunteers as in a routine vaccination course (19).

In conclusion, the sublingual/swallow IT represents a viable alternative to the injection IT both in adults and children, as recently stated by WHO in its position paper (15). Further studies need to be done to fully characterise the most appropriate eligible patients, the optimal therapeutic dose, and to assess whether SLIT is able to modify the natural course of the disease (20). Based on the studies available, the compliance with SLIT seems not to represent a problem, although a detailed instruction of patients is mandatory. Finally, it has to be remembered that local routes share with injection IT the same rationale: They act as biological response modifiers, therefore they have to be used in association with drug therapy.

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Liposome encapsulated allergens for specific vaccination



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Background

Liposomes are microscopic vesicles consisting of a lipid membrane and an aqueous inner space. The encapsulation of allergen extracts inside the vesicles results in a product with interesting properties for specific allergy vaccination. Thus, during the preclinical development of a liposome-based vaccine, it was shown that liposomes of a defined size and composition have a strong depot effect, have a significant and convenient adjuvant activity (inducing Th1-skewed immune responses) and, as judged from toxicological studies, are safe.

Study

To investigate the safety, tolerance and clinical efficacy of a biologically standardised *Dermatophagoides pteronyssinus* extract encapsulated in liposomes (DPT-LIP), a clinical development programme was initiated.

In a first step, the safety and tolerance of the product was assessed in a Phase I/II clinical trial. The study was performed in 32 patients with rhinitis, with or without asthma and monosensitised to house dust mites (HDM). This study showed that the tolerance profile was similar to that of the same extract adsorbed to aluminium hydroxide gel, albeit with a significant reduction in the number of injections during the build-up phase, and none of the patients developed subcutaneous nodules at the site of the injections. A thorough haematological and biochemical analysis of the patients confirmed the lack of toxicity of the product.

Subsequently, a DPBC Phase II/III study was performed. A total of 55 monosensitised allergic patients with asthma due to HDM were randomised to receive either placebo or DPT-LIP for a total of 18 months. The patients were clinically monitored before starting immunotherapy, after 12 and after 18 months of treatment. The environmental exposure to HDM was measured and remained constant throughout the study.

The results showed that the treatment was highly efficacious as shown by:

- A significant reduction in symptom and medication scores in the DPT-LIP group. Overall, the treatment had a clinical efficacy of 74%, measured by the reduction in symptom and medication scores after deduction of the placebo effect.
- A significant increase in the number of days free of medication and with no or only mild symptoms after treatment in the active, but not the placebo group.
- The patients in the active group had significant improvements in other assessments like cutaneous and bronchial responses as well as subjective parameters (QoL, VAS).
- The active treatment caused significant immunological effects, inducing high levels of specific immunoglobulins (mainly IgG4) and reduction of T-cell specific proliferation.

Conclusion

The clinical studies performed have shown that specific allergy vaccination with a biologically standardised extract of *D. pteronyssinus* encapsulated in liposomes is safe, well tolerated and highly efficacious in the treatment of allergic asthma due to HDM.

Latex allergy vaccination



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Hypersensitivity to latex has become a growing problem among health care workers, with a significant increase in prevalence during the last years. A double-blind, placebo controlled study using immunotherapy with a latex extract has recently been published showing good clinical results. We designed a study to investigate the tolerance and efficacy of a biologically standardised natural rubber latex (NRL) extract vaccine adsorbed to aluminium hydroxide.

The trial was designed as a double-blind, placebo-controlled immunotherapy study with parallel groups. The extract was prepared from fresh latex sap and contained allergens both from the latex serum as well as from the rubber particles. The extract had been biologically standardised according to the Nordic Guidelines.

A total of 24 patients were included; 17 of them belonging to the health care staff of our hospital and 7 were sensitised to latex due to work at home or in other jobs. Patients were selected on the basis of their clinical history and their allergy confirmed by positive skin prick test to NRL (ALK-Abelló) and controlled challenge test. Inhalation challenges were performed in a 7 m³ challenge chamber containing ultrafiltered air shaking latex gloves for increasing periods of time. During challenges total dust was monitored reaching a mean of 0.135 mg/m³. Latex allergen contents in air samples were monitored by means of an Air sentinel. In addition, methacholine tests were performed before and after challenge.

Contact urticaria was confirmed by two cutaneous challenge tests: The “use test” with latex gloves and the “rubbing test”. The first one was performed instructing the patients to wear a glove for 15 minutes on a pre-wetted hand. A latex glove was worn on one hand and a vinyl glove on the other as control. In the rubbing test, the patient’s wet forearm was gently rubbed with a latex glove for 30 seconds. In both cutaneous tests, the development of erythema, pruritus, appearance of hives and systemic reactions was evaluated after 15 and 60 minutes. Bronchial and skin challenge tests were performed at time 0 and after the end of treatment. Patients were randomly allocated to receive either NRL extract or placebo. Rhinitis and conjunctivitis

was present in 18 patients, asthma in 14 and urticaria in 13.

The treatment consisted of a 14-week build-up phase of 18 injections (the first two visits in a cluster regimen) and a maintenance of 6 fortnightly injections. The proposed maintenance dose was 5 HEP. Local and systemic reactions (SR) were carefully monitored and registered according to European Guidelines for immunotherapy (IT).

Clinical evaluation was achieved using dairy cards in which the patients scored their symptoms at the end of the working day, just after waking-up and before going to bed, as well as drug consumption.

All patients have just finished the IT course and are currently under evaluation. Consequently, randomisation codes have not been opened yet. Fifteen patients (62%) reached the proposed maximum dose. The mean tolerated dose was 3.4 HEP. From a total of 578 administered doses, 41 (7.1%) caused side effects of any intensity or nature. All SR responded promptly to treatment. No anaphylactic shocks occurred during IT.

Although further studies are needed, these data show that specific allergy vaccination with a biologically standardised latex extract adsorbed to aluminium hydroxide is safe and opens the possibility for an etiological treatment of latex allergy.

Quality of life and compliance using specific allergy vaccination



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Background

To consider the patient's perspective becomes more and more important when assessing the effect of treatment of specific immunotherapy (SIT). Therefore, we investigated the Quality of Life (QoL) and compliance during SIT over 2 years.

Method

SIT has been started in 1257 patients with rhinoconjunctivitis against grass and rye pollen allergens at 106 centres (Alutard SQ/ALK-depot SQ, ALK-Abelló). Patients assessed their QoL before (1997), after 1 (1998) and 2 years (1999) of SIT by the Rhinitis Quality of Life Questionnaire (RQLQ) of Juniper and the general questionnaire ("Alltagsleben") of Bullinger which includes 42 questions in the domains every-day life, personal field, social field, body, medical treatment and enjoyment of life on a 5-step scale. Compliance was evaluated according to the treatment protocols.

Results

The mean score over all RQLQ-domains changed from 2.93 before SIT to 1.71 after 1 year of SIT and to 1.37 after 2 years of SIT corresponding to a significant improvement of the disease-specific QoL by 1.22 score units after 1 year of SIT and by 1.56 score units after 2 years of SIT compared with the score before SIT ($p < 0.0001$). More than 75% of the patients had score improvements of 0.5, the minimal important difference for a clinical relevant improvement defined by the authors of the RQLQ. The largest score reductions were observed for the domains nasal symptoms (-1.79), eye symptoms (-1.76) and practical problems (-1.79) like impairment of sleep (-1.84) and professional work (-1.77) after 2 years of SIT.

The QoL-results corresponded well with the clinical improvement of the rhinoconjunctivitis symptoms; 93.8% of the patients improved as assessed on a scale 0-3. The general QoL improved in the subgroup of patients with a stronger impairment (32.9% with a mean score of ≤ 4 , score 5 for optimal QoL) from a mean score of 3.61 before SIT to 4.15 after 1 year of SIT and 4.28 after 2 years of SIT with largest improvements in the domains body and enjoyment of life. Only 62 patients (4.9%) after 1 year of SIT and 79 patients (7.2%) after 2 years of

SIT discontinued treatment due to compliance reasons; 1.9% after 1 year of SIT and 0.8% after 2 years of SIT discontinued SIT due to other reasons.

Conclusion

The LQC-study demonstrates that SIT improves the disease-specific quality of life of rhinoconjunctivitis patients after the first and second year of treatment, and that the general quality of life is improved for patients with a considerable impairment. The compliance with SIT applied by specialised allergists is very high.

Quality of life: Outcome of venom specific allergy vaccination



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Introduction

Although specific allergy vaccination with venom (VIT) has established efficacy for the prevention of recurrence of anaphylactic reactions to hymenoptera stings, little is known about the effects of this treatment on Health Related Quality of Life (HRQL) in these patients. We studied the effects of VIT in patients with anaphylactic sensitivity to yellow jackets using a specially developed questionnaire called the Vespid Allergy Quality of Life Questionnaire (VQLQ). This instrument consists of 14 items with 7 point response options where a higher score corresponds to better HRQL. In previous studies, it has been established that the minimum change of score which is clinically meaningful to patients (minimal important difference or MID) is 0.5 using instruments with 7 point response scales.

Methods

Patients having experienced systemic allergic reactions following yellow jacket stings, sensitised to yellow jacket venom and eligible for VIT received uniform, standardised and evidence based information, which outlined the risk of their condition and the benefits of treatment with VIT or an adrenaline self-administration device (EpiPen). Patients were then asked if they consented to be randomised to treatment with either VIT or an EpiPen in an open label study for one year. Randomised groups were matched for variables which might influence the effect of the treatment on HRQL such as baseline general anxiety as measured with a generic anxiety instrument (STAI), as well as severity of the reaction and time elapsed since the reaction. HRQL was measured with the VQLQ before the start of the treatment and after one year.

Results

Of 285 patients seen during 1997 to 1999, 101 agreed to participate, of whom 50 were randomised to one year of VIT (R-VIT group), and 51 were randomised to carry an EpiPen for a year (R-EPI group). There was no difference in initial HRQL scores between the two groups before treatment was initiated. After one year of treatment, the R-VIT group showed a statistically significant improvement in HRQL (mean VQLQ score change 0.96), whereas the R-EPI group showed a statistically significant

deterioration in HRQL (mean VQLQ score change -0.37). The resulting mean difference of change in VQLQ score between groups (1.33) was statistically significant. The improvement seen in the R-VIT group was seen in all patients regardless of gender, baseline anxiety level, or severity of or time since the sting reaction.

The proportion of patients who had a clinically important benefit ($MID > 0.5$) from being treated with VIT rather than the EpiPen was 0.68, resulting in a number needed to treat of 1.5.

Conclusion

VIT results in a clinically important improvement in HRQL in yellow jacket allergic patients in two out of every three patients receiving this treatment. The treatment is effective in all subgroups studied. Treatment with an EpiPen alone results in a deterioration in HRQL.

Allergy – Living & Learning: The European patient perception study



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The knowledge of allergy patients' perception of their own disease is inadequate, and the understanding of the impact of local environment, including family and health care system, on patients' management of their disease is insufficient. We examined the potential of telephone based survey techniques for establishing this knowledge in 10 European countries. A two-phased questionnaire developed by the help of focus groups established in 7 countries was translated into 10 languages. To ensure that the true values of the populations were restored in randomly selected populations, 75,343 telephone numbers selected for screening represented a balanced national distribution of households.

A number of 8,268 respiratory allergy sufferers were identified by the telephone screening process. A total of 85.4% accepted to participate in the survey, and 89.6% completed both phases comprising 34 questions and rating of 49 statements. Data for each country were weighted in terms of age, sex and the recorded allergy prevalence within age intervals.

The telephone survey technique allowed for establishment of random, representative samples and application of mathematical weighting procedures assured that the true national values were restored in the data set. As all interviews were performed in a standardised manner, we conclude that the telephone based survey methodology enables national representative data set to be established and compared.

Many epidemiological studies have assessed the prevalence of respiratory allergic symptoms in confined geographical locations. However, no study has yet established national prevalence data in a uniform manner representing whole countries. We analysed the "living and learning" data set in order to enable cross-national comparisons.

In 10 European countries, screening of random, representative samples of telephone numbers identified the target population aged 16 to 60. The inclusion criteria were a positive reporting of respiratory allergy to named allergens and, concomitantly, an unassisted description of appropriate symptoms. To obtain a truly representative and national prevalence of each country, the data were

weighted against the actual sex and age composition. A number of 31,065 screening interviews were performed. The nationally balanced prevalence varied significantly among the 10 countries ($p < 0.001$) from 11.7% in Spain to 33.6% in Italy. The overall weighted prevalence for Europe was 24.4%. Comparing males and females, overall, the odds-ratio was 0.874 ($p < 0.001$). For age intervals of 16-29 years, 30-49 years, and 50-60 years, the odds-ratios for males were 1.104 ($p < 0.088$), 0.827 ($p < 0.001$) and 0.658 ($p < 0.001$) respectively. The prevalence correlated inversely with age.