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Vaccines & Antibodies

Allergy vaccines – new approaches to an old concept

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Allergy vaccination (AV) consists of injecting increasing amounts of offending allergens into sensitive patients with the intention of reducing their level of sensitivity to allergens. This form of therapy was first used over one hundred years ago and until recently had not changed in principle. The vaccines themselves are now far better characterised and standardised, according to new regulatory requirements. The therapy is believed to exert its effects by a combination of means: by the induction of blocking antibodies; a switch from a T helper (Th)2 to a more Th1 allergen-specific immune response; and induction of anergy, probably via the development of allergen-specific regulatory T cells. New allergen forms and formulations are being designed with these targets in mind. Allergoids (allergens chemically modified to reduce allergenicity, but to retain immunogenicity) are becoming employed more frequently. More modern depot forms, such as those containing tyrosine or calcium phosphate, are replacing aqueous extracts and older depot adjuvants such as alum. T cell-reactive peptides and recombinant allergens or their muteins are also being studied as replacements for whole extracts and have shown some potential. Immunomodulators, such as monophosphoryl lipid A (MPL[®]), designed with defined targets in mind are now included in some vaccines and help to accelerate the process. All these measures have led to a reduction in the need for the traditional long injection schedules. The authors are very familiar in particular with the background to the use of MPL as an adjuvant. They have been personally involved in the development of this approach, which has led to a product being available for use on a regular basis in some European countries. Hence, this work is reported in considerable detail. Other similar immunomodulators, such as CpG motifs, are in development, while new targets, such as the Notch protein/receptor interaction, are exciting new developments that may eventually bear fruit. The excellent safety profile of the sublingual route of administration of allergy vaccines could lead to the wider use of AV, and locally active immunomodulators could make AV a therapy of choice for many more patients than at present.

Keywords: allergy vaccines, alum, blocking antibody, CpG, IFN- γ , IgE, IgG, IL-4, IL-5, ISS, monophosphoryl lipid A, Notch receptors, Th1, Th2, Toll-like receptors, T reg, tyrosine

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1. Introduction

It is becoming well-established that the frequency of allergic disease is increasing, especially in developed countries. The reasons for this are not clear, although a number of factors have been regarded as being responsible, and it is likely that the interaction between a combination of genetic and environmental factors leads to the allergic state [1]. In particular, modern pollutants such as diesel fuel particles, ozone and oxides of nitrogen have been implicated as adjuvants that stimulate T helper (Th)2 lymphocyte responses. Cytokines from allergen-specific

Th2 lymphocytes, such as IL-4, IL-5 and IL-13, lead to IgE production and the various inflammatory and cellular processes associated with the late phase response of allergy. In addition, it has been shown in a number of studies that children brought up in close proximity to farm animals are less likely to develop allergy [1,2]. It has been suggested that various cell wall lipopolysaccharides (LPSs) from oral–faecal bacteria stimulate the immune system to a more Th1-skewed profile from the early newborn Th2 state and/or encourage the proper development of regulatory T cells (Treg). A pronounced exposure to Gram-negative bacteria via environmental endotoxin or human microflora is observed to correlate with a lower prevalence of atopy [3]. Therefore, a modern lifestyle incorporating high standards of hygiene seems to predispose the population to an increased incidence of allergy.

Symptoms of IgE-mediated respiratory allergy, such as rhinoconjunctivitis induced by proteinaceous molecules from sources such as pollen, house dust mites, moulds and animal danders, can be of a mild and annoying nature, but are not life-threatening. However, these symptoms often worsen with time (the so-called ‘allergic march’) to more serious disease states such as asthma, which is more incapacitating and, unfortunately, still life-threatening despite the widespread use of modern drugs to treat symptoms.

These respiratory symptoms are treated by a number of means: allergen avoidance, pharmacotherapy with drugs such as antihistamines, bronchodilators and local or even systemic steroids. Pharmacotherapy is effective in many patients, but not without side effects in some. The underlying immunological lesion remains and often worsens. Immunotherapy, however, is able to modify the disease process in many patients and leads to a more profound change with a much reduced or even no further requirement for pharmacotherapy; a semipermanent cure is certainly possible after 3 or 4 years of treatment.

Following the publication of a World Health Organization Position Paper on the immunotherapy of allergic disease, the treatment is now termed allergy vaccination (AV). Alternative descriptions include specific immunotherapy and older terms such as desensitisation or hyposensitisation.

AV has been used in various ways throughout the last century, but its use has been generally limited to specialist clinics because of the complex nature of the treatment. However, recent advances in understanding the aetiology of allergy and the mechanisms involved in AV are leading to new well-controlled forms, formulations and routes of administration that should encourage much wider use of the technique in clinical practice. This may in the future lead to the use of AV outside of the specialist clinics by appropriately trained primary care physicians.

This review briefly describes the history of AV and how the newer therapeutic preparations recently introduced or being developed may help to overcome some of the earlier drawbacks of the treatment.

2. Historical perspective

2.1 Aqueous extracts

AV was first described by Curtis as ‘*the immunising cure for hay fever*’ [4]. It is likely that the rationale behind the approach was that pollen contained a toxin and, thus, injection of preparations of the offending substances in non-toxic doses would induce the formation of antitoxin antibodies. A more widely-recognised milestone was the publication in 1911 by Noon and Freeman practising at St. Mary’s Hospital, London, UK [5]. Patients with allergic rhinoconjunctivitis (hayfever) were desensitised with aqueous extracts of grass pollen using a series of subcutaneous injections of very low, but increasing doses; the maximum dose was administered just prior to the start of the pollen season. Approximately 75% of the patients showed improvement of symptoms. It is interesting that AV is still sometimes carried out using similar aqueous materials that are often mixtures of extracts from different offending sources. Although in Europe a variety of more advanced allergen forms and formulations are now utilised, in the US, aqueous formulations are still the products of choice, despite typically long courses of 20 – 30 injections spread over years. This dated procedure is clearly inconvenient, time consuming and, in terms of pharmacoeconomics, likely to be untenable in many countries.

It was previously necessary to utilise long injection courses in order to reach an effective dose because of the serious allergic effects that can occur due to the reaction of the injected allergens with preformed IgE antibodies on mast cells and basophils. Release of histamine and other mediators was seen to lead to local or serious systemic reactions that required drug and other rescue treatment. It is still presumed that during the therapy, each dose desensitises patients to such a degree that they can accept a higher dose on the next occasion. Thus, careful manipulation of the dosing schedule is required in a patient-specific way (i.e., according to the observed sensitivity to the allergens) and appropriate means must be available to treat any side effect that might occur. This led to the use of AV being restricted generally to allergy specialists or other appropriately trained medical staff. These limitations to the therapy have encouraged the development of allergen formulations that lessen the likelihood of side effects and reduce the number of injections required.

2.2 Depot adjuvants

In 1926, Glenny showed that alum-precipitated diphtheria toxoid was more immunogenic than toxoid alone [6]. This technique was applied to AV by Sledge in 1938 [7] to induce the production of so-called ‘blocking antibodies’, and alum salts such as aluminium hydroxide are widely used as depot adjuvants in AVs mainly outside the US even today. Insoluble depot adjuvants such as alum serve two purposes. First, they promote a heightened immune response to the adsorbed allergen extract. Second, they reduce the likelihood of side effects from the treatment by releasing the allergens slowly and, thus,

allowing a reduced dose of allergen extract to provide the same benefit as higher doses used in non-adjuvanted vaccines.

This information encouraged a search for more effective adjuvants, such as water-in-oil emulsions and other materials; although effective, most were discontinued because of serious local reactions.

Alum has been a mainstay adjuvant of AV for many years, but recently some safety concerns have emerged, such as various types of local reactions or an implication in Alzheimer's disease [8]. This is of particular significance for AV, where sometimes as many as 12 – 18 injections may be given annually. Other more acceptable modern depot adjuvants that are more soluble in physiological conditions are now being used, for example, calcium phosphate and the naturally occurring amino acid tyrosine, which is weakly soluble at neutral pH, but adsorbs allergens effectively and slowly dissolves following subcutaneous injection, with a half-life of ~ 48 h. It may be of significance that alum is well known in experimental conditions to be a Th2 lymphocyte-inducing adjuvant [9] and, thus, conceptually at least, is inappropriate for the treatment of a condition that is already due to a Th2-skewing of a specific immune response.

3. Mechanisms

3.1 Original theories

It was thought for many years that the induction of blocking antibodies by AV was the key to successful treatment. It was shown that the use of a highly immunogenic preparation was associated with efficacy in large groups of patients. However, a direct correlation between the level or rise of antibody, or ratio of antibody, between IgG and IgE could not be established on an individual patient basis.

The blocking antibody theory was rekindled by the discovery of different IgG subclasses, in particular IgG4 and IgG2, but the direct correlation still could not be established. It also seemed unlikely that IgG antibody in the circulation could block the reaction between inhaled allergens and IgE on mast cells in the nose and lung, although secretory IgA antibody would perhaps be more appropriate. Other possible functions of IgG were suggested, such as feedback on IgE production, although the problem with this theory was that IgE commonly rises in the first year of AV, even though the patient can still obtain remission from allergic symptoms.

3.2 Existing theories

3.2.1 Th1/Th2 imbalance restoration

There is a widely held view that IgE-mediated allergy is due to an imbalance between allergen-specific Th1 and Th2 lymphocytes, with an excess of Th2 activity. Cytokines from Th2 cells, such as IL-4, -13 and -5, lead to the induction of IgE antibody from B cells and the late phase inflammatory response of allergy. The latter occurs ~ 4 h after challenge and is characterised by infiltration of cells, in particular eosinophils, to the site of allergen deposition. Some cell infiltrates

may add to the inflammatory lesion, although there is now evidence that eosinophils, in particular, may have a repair function. Evidence has suggested that AV can at least partially restore the balance to a Th1 > Th2 state [10] and, thus, there should be a reduction in the late phase response and eventually less stimulation of the production of IgE-producing B cells.

3.2.2 Regulatory T cells and anergy

It has been known for many years that blast cell formation *in vitro* from allergen challenge (the lymphocyte transformation test) is eventually reduced by AV. In addition, it was believed that lymphocytes, then called 'suppressor T cells', were responsible. Recently, the presence of so-called 'regulatory T cells' has been established, so it is tempting to equate the two ideas. It has been suggested that the level of T reg that tend to produce anergy of allergen-specific T cells could be part of the desensitisation process in AV. The involvement of IL-10 in this phenomenon has also been highlighted [11]. It has been shown that immune deviation towards T reg cells plays an important role in AV. Multiple suppressor factors from these induced cells, such as IL-10 and transforming growth factor (TGF)- β , are associated with the induction of non-complement fixing non-inflammatory blocking IgG4 and IgA antibodies, respectively. IL-10 and TGF- β are involved in suppression of Th2 cells in particular, but they also have various suppressor influences on effector cells such as mast cells, basophils and eosinophils.

3.2.3 Blocking antibody

The blocking antibody theory has recently resurfaced [12,13], probably due to the ability of investigators to measure the induction of subclass IgG antibodies against individually cloned or purified allergens, as opposed to the earlier work with whole extracts containing many allergens to which individual patients would have varied antibody responses. The ability to dissect the responses of an individual in this way has certainly led to the observation of better correlation between relief from symptoms and IgG subclass antibody responses and has given credence to the notion that the induction of non-IgE antibodies might be at least partly responsible for some of the benefits of AV.

IgG4 antibodies in particular have been associated with successful vaccination. Although the original concept of blocking access to IgE-sensitised mast cells may not be so important, more complex theories are under discussion. IgG4 may prevent the binding of allergen on the B cell receptors (CD23) and, thus, IgE boosting from environmental challenge can be ablated.

4. Delivery systems

Allergy vaccines are often provided as 'named patient products' (specials) by manufacturers, because of the vast number of sensitivities that allergists wish to treat. Even so, in Europe, reputable manufacturers prepare these in inspected Good

Manufacturing Practice facilities using similar technologies and control procedures as for licensed products. It is likely that these mixtures are less effective than single allergen extracts because of dilution effects; therefore, the number of allergen extracts in a combined vaccine is usually kept to a minimum.

4.1 Aqueous

Aqueous extracts of allergens were for many years the main formulations used, as described above. In earlier times, these were very crude materials with scant quality control, although recently they have been made on a sound pharmaceutical basis. In particular, a great deal of attention has been paid to the standardisation of such products, with batch-to-batch consistency and proven stability being required by regulatory authorities. These requirements have of course been extended to all allergen formulations.

4.2 Depot

Depot formulations such as alum and tyrosine adsorbates have been described above. These continue to provide safer products, as the allergen extract is released slowly at the injection site and adjuvant properties of these depot materials give a more powerful immunological stimulus.

4.3 Particulates

There have been many attempts to develop liposomes, microspheres and immunostimulating complexes containing allergens [14,15]. Some have actually progressed to clinical trial and were effective, but did not seem to provide any advantages over depot forms, despite the possibility that some of the components of the formulation might be Th1 cell directing. Microspheres were studied for their potential to be used subcutaneously or orally, as there was evidence that they would be taken up by M cells overlaying Peyer's Patches [16]. It was suggested that stimulation of the common mucosal immune system by this means would lead to amelioration of symptoms at a remote site such as the nose and lungs. However, little further progress is apparent from the absence of more recent publications on these subjects.

5. Allergen forms

5.1 Extracts

For many years the only forms of allergens used were unmodified aqueous extracts from allergen sources, such as pollens, mites, moulds, danders and so on, which contained a mixture of many molecules, some of which were allergenic and some not. Eventually, various forms of purification led at least to the removal of low molecular weight materials (allergens are mostly > 10 kDa molecular weight, except for Amb a 5 from ragweed pollen).

5.2 Allergoids

Carter was the first investigator who tried to make his extracts safer to use by modifying them through chemical means [101].

The procedures used were analogous to those then being introduced to make toxoids from toxins by formaldehyde treatment. The new modified allergens were little used at that time, but Marsh, Patterson and Johansson reintroduced the principle in the 1970s [17-19]. Formaldehyde and glutaraldehyde were studied as modifying agents, with the glutaraldehyde-modified allergen extracts being the first to be introduced into clinical practice in Europe. Products made by this process and adsorbed onto alum or tyrosine in particular are now widely used in Europe. Glutaraldehyde, a bifunctional reagent, modifies allergens in such a way that their reactivity with IgE is extensively reduced (providing a safety bonus), while the ability to produce an IgG4 response to some epitopes on the allergens is little affected and efficacy maintained. It is now believed that the T cell reactivity of allergens may be at least partly responsible for the therapeutic effects. As it is the primary structure of allergens that is important for reactivity with T cells, and as the primary structure of the allergenic proteins is likely to be retained, the efficacious properties of allergoids should be relatively unaffected by the modification process.

5.3 Cloned allergens

There has been a massive expansion of literature describing allergens made by various recombinant technologies [20]. It is tempting to suggest the use of such molecules for AV, and the advantages are obvious. First, one could make cocktails of only those single allergen molecules to which patients are sensitive on an individual patient basis. Second, one would have a source of reproducible, easily standardised molecules. Cloned allergens have been used as tools to dissect immune responses at the antibody (B cell) and T cell epitope level; however, although clinical experimentation has begun, there are many hurdles that may prevent their use on a regular basis for AV. It is the complexity, number and cost of individual, properly licensed molecules representing allergens, and possibly their isoforms, that would be required that create a possibly insurmountable problem for the manufacturers. In addition, if individual cocktails of cloned allergens are to be prepared for patients depending on their sensitivity profiles, then the products are designated 'specials' or named-patient products and cannot be properly licensed.

Although it is possible that a single or standard combination of cloned allergens could be used, it has to be asked if there is any *a priori* reason why this should be any more effective or safer than a whole, properly controlled and standardised product from natural sources and whether the added cost of development and, thus, price of product could be justified or accommodated by healthcare systems.

5.4 Muteins

One of the most interesting developments in the field of recombinant allergens has been the preparation of mutein forms by site-directed mutagenesis. Some very elegant experiments have identified the IgE antibody combining sites of some allergenic proteins, usually based on the tertiary

structure [21]. Replacement of individual amino acids within these sites has led to the production of molecules that do not react with IgE antibody and, hence, are safer to use, but still react with T cells and should provide effective treatment [22].

Many allergens exist in a variety of isoforms, with only small structural differences that contribute to their different isoelectric points. Members of the same allergen family of isoforms do not have identical immunological characteristics as far as antibody epitopes are concerned, but usually have similar T cell epitopes. Naturally occurring isoforms sometimes have similar characteristics to the artificial muteins and could be considered for inclusion in AV.

Some of the limitations for use apply to muteins as for other cloned allergens, but the added safety bonus could provide more impetus for their further development.

5.5 Peptides

It has been believed for some time that the T cell reactivity of allergens is important for AV. Peptides containing T cell epitopes, but lacking in IgE reactivity, were studied in an attempt to produce safer and more effective vaccines. The peptides used were derived from the known structure of Fel d 1, the most important allergen from cats. Large peptides were required in order to encompass the various T cell epitopes from patient to patient [23]. These peptides were so large that they were able to induce *de novo* specificity IgE antibodies in some subjects and also induce unusual, serious, late phase adverse events. This approach has been better refined recently [24] and overlapping peptides from Fel d 1 were screened in terms of T cell epitope content. A mixture of relevant peptides has been shown to have a degree of efficacy, although appropriate dosing to avoid generalised 'late reactions' appears to have not yet been established.

Some of the most convincing studies in the use of peptides have been carried out with peptides from the major allergen of bee venom, phospholipase A2 (PLA2). Three short peptides were chosen on the basis that they stimulated T cell clones from allergic and non-allergic subjects. It was shown that whole allergen vaccination induced anergy in peripheral T cells to PLA2 and to the three peptides. Subjects allergic to bee venom were treated with a mixture of these three peptides by a rising dose schedule [25]. Tolerance to the treatment was good, probably because IgE epitopes were not present. The subjects could subsequently tolerate an injection of PLA2 equivalent to one bee sting. T cell proliferation to both PLA2 and the peptides was abrogated, as well as the production of IFN- γ and IL-2, -4 and -5, suggesting that induction of T reg could lead to anergy in allergen-specific T cells. Some subjects could subsequently tolerate a bee sting.

Peptides clearly hold some promise, but there is some way to go before they will be available for general use. The peptide approach could be helpful in cases where there is only one or very few major allergens within a source material. Cat hair and bee venom are excellent examples of this situation.

6. Immunomodulators

6.1 Immunostimulatory sequences

Molecules that act to induce preferentially a Th1 lymphocyte response are potential candidates for modulation of the immune responses in allergy. One of the most fascinating recent developments has sprung from the observation that during immunisation of mice with bacterial DNA, certain bacterial immunostimulatory sequences (ISSs, or CpG motifs) can act as Th1 adjuvants, as demonstrated by antibody and cytokine induction. Following gene immunotherapy with plasmid DNA (pDNA) encoding β -galactosidase, CD4⁺ T cells were stimulated with antigen *in vitro*, resulting in IgG2a induction and production of IFN- γ , but no IL-4 or -5 was released. In the same experiment, IgE and IgG1 were induced by β -galactosidase in alum, but in contrast, IL-4 and -5 were released and no IFN- γ was detected. The Th1 response was found to result from a non-coding sequence (ISS) in the backbone of the pDNA [26]. Advantage has been taken of this by coupling non-coding ISSs directly with single recombinant allergens, such as Amb a 1 from ragweed pollen [27], or by co-administration in the case of Cry j 1 and Cry j 2 from the pollen of Japanese cedar [28]. Although experimental data suggest that these are appropriate forms for AV, the practicalities associated with the number of products required and the cost of obtaining full data for registration of each may be prohibitive. Clinical work is ongoing to prove the effectiveness of the potential products and to try to reduce the number of injections required for efficacy.

6.2 Killed bacterial cells: *Mycobacterium vaccae*

Studies have been progressing for some years now to examine the utility of dead mycobacteria in the treatment of allergy. The original concept was that this might direct the immune response away from the Th2-skewed state or induce the production of T reg. A tenuous link here can be made with the use of complete Freund's adjuvant in animals. This adjuvant contains mycobacteria, which tend to divert the adjuvanted immune response to the included antigen with a Th1-like bias. Results in humans have been equivocal, which is not surprising as the studies have been done without the inclusion of an accompanying allergen to provide the specific challenge that the T cells are likely to require [29]. Isolation of the active moiety from the cell walls could provide a more acceptable agent than the whole dead cells.

6.3 Monophosphoryl lipid A

The most advanced work in the development of novel immunostimulants for AV has employed monophosphoryl lipid A (MPL[®]) [30]. It is well known that LPSs are good adjuvants for the production of a Th1 response, but considerations of toxicity have limited their use until recently. MPL is the first member of a new generation of soluble adjuvants derived from bacterial cell walls and originally designed for use with bacterial, viral and oncology vaccines. MPL has the potential to

Table 1. Immunological changes induced by allergy vaccination adjuvanted by MPL®.

Immunological effect	Reference
Increased specific IgG antibody for allergen extract	[33]
Increased specific IgG ₄ to major allergens	[12]
Decrease in seasonally induced IgE antibody	[33]
Increase in IFN- γ from specific T cells	[38]
Decrease in IL-5 from specific T cells	[38]
Decrease in CD23, CD54, HLA-DR-II on B cells	[39]
An initial increase then a decrease in specific lymphocyte transformation	[40]
Reduced skin test sensitivity to specific allergen	[33]
Participation of IL-12	[41]

HLA: Human leukocyte antigen.

enhance the status of AV because of its capacity to induce the production of a more Th1 rather than Th2 cell profile of cytokines. MPL is derived from the cell wall of *Salmonella minnesota*, which relates to the observations of an inverse relationship between Gram-negative exposure in early childhood and atopy. MPL is detoxified by acid and alkali treatment and highly purified by high-pressure liquid chromatography. The well-characterised product is composed of a number of analogues (congeners) having different fatty acid side chains.

The mechanism whereby MPL is likely to assist desensitisation is complex, but is under investigation. MPL exerts its effect as it is derived from LPS and, although its toxic properties have been attenuated, its immunological effects are retained. LPS is a pathogen-associated molecular pattern (PAMP), which is recognised by pattern-associated antigen-presenting cells (APCs). For a molecule to be recognised as a PAMP by an APC, it must have a structure that is shared by a large number of pathogens, but is not found within the human body. PAMPs are typically substances originating from bacteria, such as LPS and certain other molecules. LPS and MPL (regarded as 'danger signals') are primarily recognised by the Toll-like receptor (TLR)4 for PAMPs, although there is some evidence that the TLR2 pathway is also involved [31]. This initiates an intracellular signalling cascade, which activates nuclear factor- κ B, a classic pro-inflammatory gene transcription regulator. These events lead to the development of the APC into a type 1 dendritic cell (DC1), which is able to drive the Th1 response. Once a dendritic cell encounters antigen and a PAMP signal, it starts to mature and migrates to a draining lymph node where it becomes active. Thus, an antigen signal is required concomitantly with the MPL stimulus.

Mature DC1 cells present antigens to T cells. Cytokines, in particular IL-12, produced by the DC1 cells influence the T cell to mature into a Th1 phenotype. The Th1 cell produces IFN- γ , which downregulates the Th2 cell population and, thus, reduces the production of IL-4, -5 and -13. IL-10, which may well be associated with the induction of T reg and

the eventual anergy believed to be a part of the desensitisation process, is also induced by MPL [31].

Immunological changes brought about during the course of treatment with MPL-adjuvanted AV have been published by a number of authors and are consistent with those actions believed to be involved in the desensitisation process (see Table 1).

It is of interest that experimental work has indicated synergy with antigens formulated with tyrosine and MPL in producing a Th1 response [32]. Allergy vaccines have been developed containing various chemically modified pollen extracts, such as those from grass, birch tree, olive tree, wall pellitory and ragweed, which possess reduced reactivity with IgE antibody (allergoids) and are adsorbed to tyrosine as a depot adjuvant. This provides the specific immunological signals, modulated by the addition of MPL. Clinical trials have proved the effectiveness of the new products, and both controlled clinical trials and postmarketing surveillance studies have confirmed a satisfactory safety/efficacy profile of the vaccines [33,34]. More than 60,000 courses of the vaccine have now been used in three European countries. The major advantage of an MPL-adjuvanted vaccine is that a treatment course of only four annual injections is required prior to the pollen season, compared with the many injections, often on a continuous basis, usually used to provide an effective treatment with 'traditional' vaccines.

6.4 Notch receptor agonists

Notch is a cell surface receptor present on T cells that is activated when it encounters a Notch binding protein present on APCs. If T cell antigen recognition is combined with Notch pathway signalling, then the immune response to the antigen is switched off via the release of immunosuppressive cytokines [35]. The formulation of Notch binding proteins as agonists with allergens could provide a means of switching off the undesired type of immune response to these allergens. Research into this possibility is underway and may provide exciting new approaches to the treatments of allergy.

7. Routes of administration

AV has most commonly been administered by subcutaneous injection, although some earlier work using oral dosing has been carried out and was shown to be poorly effective [36]. More recently, the sublingual route has been shown to be effective [37] and to have such a good safety profile that self-administration by patients has become popular in some countries. Although many would argue that dosing by this route might not be as effective as by injection, it is conceded that the convenience, compliance and safety profile are convincingly superior and, thus, it is becoming the route of choice for many patients. The incorporation of immunomodulators in order to gain efficacy could make the sublingual route one that could extend the use of AV to a greater number of patients and to the prescribing of such therapy in primary healthcare.

8. Expert opinion and conclusion

AV is a method of treating respiratory allergy, which has a particular advantage in correcting the underlying immunological imbalance that can lead to a semipermanent cure after a few years of treatment. Its use has generally been restricted to allergy specialists who can manipulate the dosing according to the medical requirements of individual patients and who are trained to deal with any anaphylactic side effects that could rarely occur during treatment. Other limitations to its use are the inconveniences of many injections and visits to the surgery.

New treatment formulations are now being developed and some allergy vaccines are designed especially on the basis of the mechanisms believed to be responsible for the desensitisation process and are already available in some countries. These formulations are particularly useful in reducing the numbers of injections. AV by mouth (sublingual immunotherapy) is gaining support. These newer approaches incorporating more convenient therapy and routes of administration, coupled with the safety benefits of standardised vaccines, are likely to lead to a revival in the use of AV to treat and maybe one day prevent the development of allergic disease and prevent further growth of this debilitating and sometimes fatal condition.

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Patent

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