

Recombinant Bet v 1 vaccine for treatment of allergy to birch pollen

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Therapeutic vaccination is the only disease modifying allergy treatment. Recombinant allergen vaccines represent defined component vaccines and are advantageous compared to allergen extract vaccines because of their well defined and measurable allergen content. As the major birch pollen allergen Bet v 1 is the dominant disease-eliciting allergen in birch pollen Bet v 1 vaccines based on GMP produced recombinant (r)Bet v 1 have been developed for treatment of birch pollen allergic patients. Three vaccines comprising hypoallergenic rBet v 1 derivatives have in clinical trials been shown to improve allergic symptoms and to favourably modify the immune response to Bet v 1. In a phase II trial, vaccination with rBet v 1 resulted in reduced rhinoconjunctivitis symptoms and rescue medication compared to placebo. Vaccination with rBet v 1 formulated as tablets for sublingual administration revealed clinical relevant efficacy in rhinoconjunctivitis patients. The positive results imply that rBet v 1 vaccines constitute a therapeutic alternative for birch pollen allergic patients.

Introduction

Allergic diseases affect hundreds of millions of patients worldwide and constitute a major burden to society. The most common type of allergy is caused by IgE antibodies raised towards otherwise harmless environmental antigens, defined as allergens.¹ The allergic symptoms range from mild rhinoconjunctivitis to potentially life-threatening asthmatic exacerbations. It is estimated that 10–30% of the population in the US² and at least 20% in Europe suffers from allergic rhinitis.³ According to the World Allergy Organization report in 2008, approximately €14 billion are spent globally each year on allergic rhinitis and 300 million persons worldwide are estimated to suffer from asthma. The high incidence of allergic diseases has highlighted the need for efficient treatments.

Immunoglobulin (Ig) E mediated allergy (also referred to as type 1 allergy) can be divided into a sensitization phase and an effector phase.⁴ Sensitization to an allergen involves the mounting of a T helper (Th) 2 type of immune response and production

of allergen-specific IgE. The cause of this improper immune response to innocuous environmental allergens is a matter of extensive research, but insufficient immune regulation is considered as a major contributing mechanism.⁵ Instead of induction of peripheral tolerance, allergen-specific Th2 clones producing typical Th2-cytokines like interleukin (IL)-4, IL-5 and IL-13 expand and immunological memory is established during the sensitization phase. The allergen-specific IgE that are produced bind to high affinity receptors, FcεRI, expressed on the surface of mast cells and basophils. In the immediate effector phase IgE-FcεRI complexes are crosslinked upon re-exposure to the sensitizing allergen. This results in degranulation and activation of effector cells causing symptoms typical for the immediate allergic reaction, i.e., rhinitis, conjunctivitis and asthmatic reactions. Late-phase reactions are triggered by continuous activation of allergen-specific Th2 cells and may initiate an allergic inflammatory cascade that eventually leads to chronic disease, e.g., persistent chronic asthma, rhinitis and atopic eczema. The allergic inflammation is initially characterized by tissue infiltration and activation of Th2-cells and eosinophils and at a later stage by the involvement of several pro-inflammatory cells of both the adaptive and the innate branch of the immune system, as well as tissue resident cells.⁶

Allergic disease may be treated by allergy vaccination, also known as allergen-specific immunotherapy. Allergy vaccines are today exclusively administered in therapeutic vaccination protocols. Symptom relief by allergy vaccination is obtained upon repeated administration of allergen to the sensitized patient. Thus the pathologic immune response towards the disease-eliciting allergen has to be reprogrammed to obtain a healthy immune response to the allergen. The mechanisms for how this is achieved are not fully understood. One main hypothesis is that T-cells are the preferential targets of successful allergy vaccination. The proposed mechanism may either involve induction of a state of anergy/deletion of allergen-specific Th2 cells or immune deviation, i.e., a shift from a predominantly Th2-like to a more Th1-like phenotype.⁷ Allergy vaccination has also been reported to induce regulatory T-cells (Treg) and the regulatory cytokine IL-10, suggesting a mechanistic role for Tregs.^{8–10} Another main hypothesis stresses the importance of the humoral immune response and “blocking antibodies” for resolving the allergic symptoms. Thus it has been shown in several studies that allergen-specific IgG, that may potentially prevent allergen-IgE interactions, are generated during allergy vaccination^{11–15} (Fig. 1).

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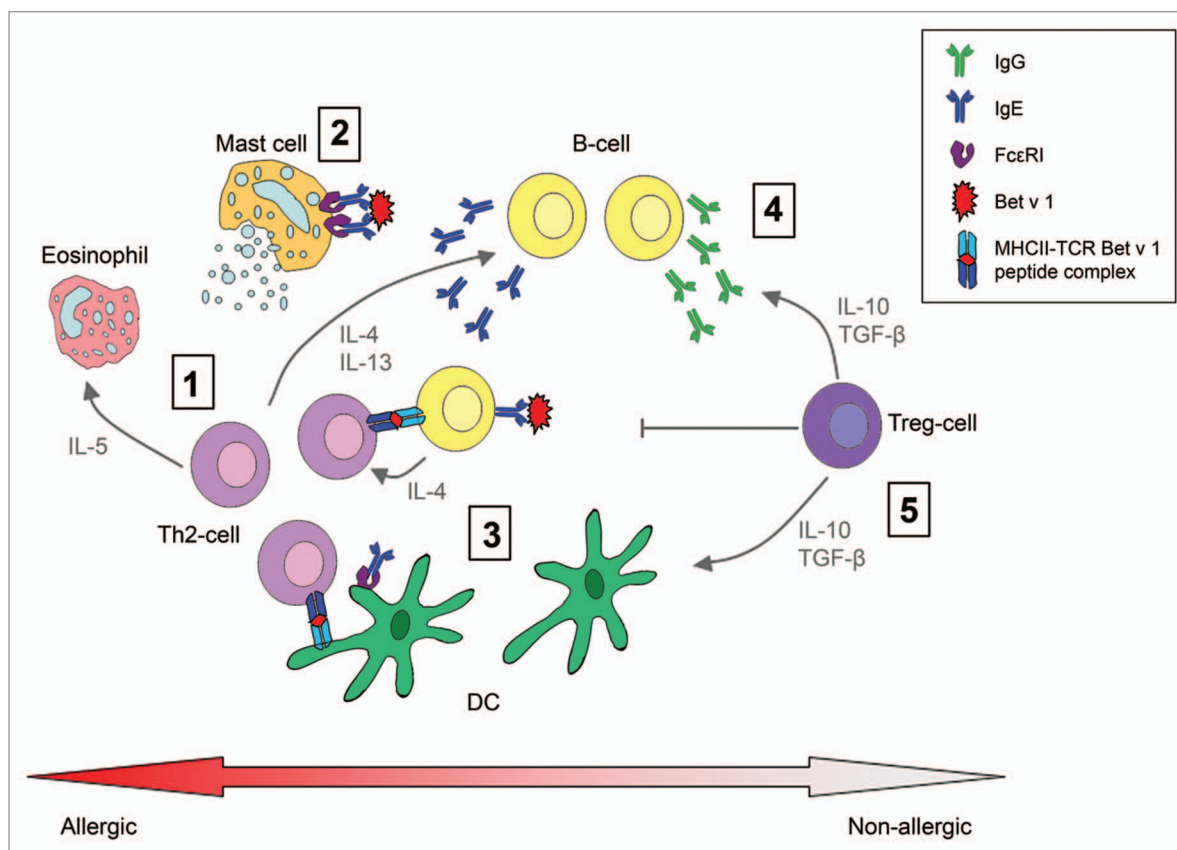


Figure 1. Proposed mechanisms of allergy vaccination. IgE mediated allergy to birch pollen is dependent on Th2 cells and cytokines. Allergen-specific Th2 cells secrete IL-4 and IL-13, which promote class switching to IgE and clonal expansion of naive and Bet v 1 specific memory B-cells. IgE at the surface of B-cells and bond to IgE receptors on other antigen presenting cells, like dendritic cells (DC), facilitates antigen presentation of Bet v 1, resulting in activation and clonal expansion of Bet v 1 specific Th2-cells. Upon cross-linking of Bet v 1 specific IgE bond to high affinity IgE receptors (FcεRI) on mast cells, the mast cells degranulate and release mediators and cytokines leading to immediate allergic reactions. Mast cell mediators and Th2 cytokines (e.g., IL-5) also promote allergic inflammation, characterized by Th2 cells and eosinophils. In contrast, Treg cells and regulatory cytokines (IL-10 and TGFβ) control the allergic immune response by suppression of Th2 cells, mast cells and B-cell IgE-production, and by induction of allergen-specific IgG. Allergy vaccination inhibits the allergic response and promotes a healthy non-allergic immune response by several mechanisms: (1) Suppression of Th2 cells and cytokines, skewing of Th2 to Th1. (2) Decreased mast cell numbers and mediator release. (3) Decreased IgE facilitated presentation of Bet v 1, decreased number of Th2 promoting and proinflammatory DC:s, increase of Treg inducing DC:s. (4) Decreased seasonal increase of Bet v 1 specific IgE and induction of Bet v 1 specific IgG. (5) Induction of Treg cells and regulatory cytokines.

At present allergy vaccination is performed with extracts prepared from natural allergen sources. The allergen extracts may be adsorbed to an aluminium salt (alum) and administered by subcutaneous injections (subcutaneous allergen-specific immunotherapy, SCIT). Alum functions both as an adjuvant and a depot to prevent immediate systemic spread of the allergen. Alternatively the vaccine may be administered via the sublingual route (sublingual allergen-specific immunotherapy, SLIT). Particularly in Europe this route has become widely accepted during recent years, as an increasing body of evidence has shown that SLIT is efficient and exhibits a milder side effect profile as compared to SCIT.¹⁶ Although allergy vaccination has proved efficacious, as performed today it possesses some main drawbacks.^{17,18} Long treatment periods (up to 3–5 years) are required and local or systemic adverse side-effects may occur.¹⁹ To solve these problems, alternative vaccination strategies have been proposed. When developing novel allergy vaccines the target allergen should be well-defined and therefore recombinant

allergens have been proposed instead of extracts of the allergen sources.²⁰

Recombinant allergens are expected to be introduced into clinical practice as an alternative to allergen extract-based vaccines.²¹ The major birch pollen allergen Bet v 1 is one of the first recombinant allergens that has been extensively studied for allergy vaccination. It is an excellent candidate for this purpose. Allergy to birch pollen is characterized by increased production of allergen-specific IgE and tissue eosinophilia, which gives rise to symptoms in upper and lower airways. It is a clinically relevant allergen, as in cold and temperate regions birch pollen allergy affects approximately 20% of the population in exposed areas, e.g., in central and northern Europe.²² Importantly, Bet v 1 is the disease eliciting allergen in approximately 90% of birch pollen sensitized patients²³ and Bet v 1-crossreacting allergens also cause symptoms to related tree pollen and foods.^{24–28} Finally, Bet v 1 is a well-studied allergen for which numerous data on the molecular structure as well as

Table 1. Trials employing rBet v 1 or rBet v 1 derivatives to treat birch pollen allergic patients

Vaccine	Route of administration	Clinical trial	Author	Reference
rBet v 1 trimer and rBet v 1 fragment mix	Subcutaneous (s.c.)	Phase II Placebo controlled	Niederberger, et al. Reisinger, et al. Gafvelin, et al. Purohit, et al.	67, 79, 81, 82
rBet v 1 Folding variant	s.c.	Phase II/III Placebo controlled Compared to extract	Kettner, et al.	83, 85
rBet v 1 (wild-type)	s.c.	Phase II Placebo controlled Compared to extract and natural Bet v 1	Pauli, et al.	77
rBet v 1 (wild-type)	Sublingual	Phase II Placebo controlled Three doses	Rak, et al.	87

Table 2. Bet v 1 vaccine related patents

Description ¹	Inventor	Patent holder ²	Patent info ³	Year ⁴
Bet v 1 (and related tree pollen allergens) recombinant molecules	Breiteneder, et al.	Biomay AG	AU1343695 US 5693495	1990
Bet v 1 (and related tree pollen allergens) T-cell epitope peptides	Ebner, et al.	Biomay AG	AU5411594 WO 9410194	1993
Method for purification of rBet v 1 insoluble aggregates	Cromwell and Fiebig	MERCK Patent GMBH	PT1315740 WO0220559	2000
Method for preparing hypoallergenic rBet v 1	Zukk and Fiebig	MERCK Patent GMBH	RU2004129282 WO03072601	2002
Recombinant Bet v 1 allergen mutants, methods and process thereof	Holm and Ferreras	ALK Abéllo	WO03096869	2002
Method for selecting immunotherapeutic preparation	Ernst and Jakobsen	Novozymes AS	US2008254041	2003
Hypoallergenic Bet v 1 variants	Mistrello and Zanota	Lofarma	EP2172215	2005

¹Short description of patent. ²Patent applicant. ³Publication info reference. ⁴Year of priority date.

extensive characterization of its immunological properties are available.²⁸⁻³³

Key Issues

- Allergy vaccination is the only clinically available treatment that targets the cause of allergic disease and leads to long-lasting relief of allergic symptoms.

- As performed today allergy vaccination is time-consuming, resource demanding and linked to a risk for adverse side effects.

- Allergen extracts commonly used as allergy vaccines consist of a mixture of allergenic and non-allergenic material that may be difficult to standardize and new treatment-induced sensitizations are a potential risk.

- Recombinant allergens are allergenic proteins produced by molecular cloning techniques, with structural and immunological properties comparable to the corresponding natural allergen.

- Recombinant allergens may be genetically modified to create allergen derivatives. A number of strategies have been employed to obtain safer and more efficient allergy vaccines based on recombinant allergen derivatives.

- Recombinant (r) Bet v 1 produced under GMP conditions is available as reference material and for application in SCIT and SLIT.

- Application of rBet v 1 vaccines in clinical SCIT and SLIT trials has generated promising results.

Current Treatment Options

Allergy treatment of today mainly focuses on symptom relief, either by blocking or reducing release of critical mediators of the allergic reaction (with e.g., antihistamines, antileukotriens, cromones) or by inhibiting the allergic inflammation (corticosteroid treatment). A prolonged reduction of allergic symptoms may be achieved by treatment with omalizumab, a monoclonal antibody binding to circulating IgE and preventing subsequent binding to FcεRI on effector cells.³⁴ Both pharmaceutical treatment and anti-IgE targets general mechanisms in the allergic reaction common for different allergies. In contrast, allergy vaccination will treat allergy towards a specific allergen or allergen source. It is also the only treatment in use that changes the natural course of allergic disease and gives a long-lasting relief of symptoms.³⁵⁻³⁷

Unlike pharmaceutical treatment, vaccination can reduce allergic inflammation in the airways and protect against development into chronic disease.^{17,38} Allergy vaccination has been practiced for 100 years, since it was first introduced by Noon in 1911 as a treatment for pollen-induced hay fever.³⁹ The safety, efficacy and long-lasting effect of SCIT has been documented for insect venom-induced anaphylaxis,^{40,41} pollen-induced rhinoconjunctivitis⁴² and for allergic asthma.⁴³ For treatment of birch pollen allergy, pollen extracts are used in clinical practice. Subcutaneous injections have proved to efficiently reduce symptoms and medication during the pollen season, as compared to placebo treatment.^{44,45} Birch pollen allergic patients have also been treated with SLIT, resulting in improved medication and symptom scores as well as pulmonary function during the pollen season.^{46,47}

Natural birch pollen extracts are manufactured and marketed by several companies. Due to the heterogenic composition of the extracts it may be difficult to standardize the allergen content and to ensure the same clinical efficacy between batches.^{48,49} Therefore allergen extracts have to be standardized to guarantee quality in terms of safety and potency of the vaccine. The challenge is that there are no common standards for measurement of the allergenic and other components in allergen extracts from different manufacturers. Therefore comparative information on major allergen content in pollen vaccines is generally inadequate.⁵⁰ The CREATE project, financed by the European Union, set out to introduce standardized techniques to quantify major allergen content in extracts.^{51,52} Recombinant Bet v 1 was shown to be excellent for use as a reference allergen, as it is structurally indistinguishable from its natural counterpart.^{53,54} The CREATE consortium has selected an rBet v 1 (Bet v 1.0101) produced by Stallergenes under GMP conditions as international reference for natural Bet v 1-like molecules.⁵⁴ This will permit standardization of birch pollen allergen vaccines for Bet v 1 and allow comparisons between different manufacturing sources.^{51,54,55} Another problem linked to the complex protein content of allergen extracts is that vaccination may lead to new sensitizations.⁵⁶ It has been reported that patients monosensitized to Bet v 1 can develop sensitization to other birch pollen allergens, e.g., Bet v 2 and Bet v 4, after treatment with birch pollen extract vaccines.⁵⁷ Moreover the extracts may contain other compounds that may influence the immune reaction in an unpredictable way. For example the endotoxin content in extract-based allergy vaccines has been shown to vary considerably between different standardized vaccines.⁵⁸

Design

Bet v 1 is one of the first allergens to be formulated as a recombinant human allergy vaccine. Both the wild-type allergen and hypoallergenic derivatives of Bet v 1 has so far been used in clinical trials (Table 1).

The DNA sequence encoding Bet v 1 was originally reported in 1989.⁵⁹ The Bet v 1 gene was then engineered into bacterial expression systems in order to produce rBet v 1.^{60,61} Immunological characterization of rBet v 1 expressed as a non-fusion protein revealed that the recombinant protein was comparable to natural Bet v 1 regarding its capacity to bind to rabbit anti-Bet v

1 antibodies and IgE antibodies from birch pollen sensitized patients.⁶⁰ Furthermore the recombinant Bet v 1 stimulated Bet v 1 specific T-cell clones and triggered histamine release from basophils derived from birch pollen allergic patients at similar magnitudes as its natural counterpart.⁶⁰ In nature several different isoforms of Bet v 1 exist, as the birch genome contains at least seven Bet v 1 encoding genes.^{62,63} Some of the isoforms have been described to be less allergenic, i.e., possess reduced IgE-binding capacity, and therefore are natural hypoallergens.^{62,64,65} The rBet v 1 produced under GMP and used as a biological reference preparation is based on the Bet v 1.0101 isoform,⁵⁴ equivalent to the originally cloned and expressed Bet v 1a isoform.^{53,59,60} This isoform is the most abundant one found in birch pollen extracts.⁶⁶ A number of rBet v 1 vaccine related patients have been registered (Table 2).

Two genetically modified Bet v 1 hypoallergens were the first recombinant allergen vaccines to be tested in allergic patients.⁶⁷ The rationale for applying hypoallergens, i.e., allergens with a reduced capacity to bind IgE but retained immunogenicity, is to reduce the risk of treatment induced immediate allergic reactions.²⁰ The two rBet v 1 hypoallergens consisted of a trimer with three Bet v 1 molecules linked and expressed as one protein ("trimer")⁶⁸ and an equimolar mix of Bet v 1(1-73) and Bet v 1(74-159) fragments covering the full sequence of Bet v 1 ("fragment mix").⁶⁹ The hypoallergen vaccines were expressed in a prokaryotic expression system employing the *Escherichia coli* strain BL21 (DE3), which overexpresses the engineered hypoallergen genes (fragments and trimer) under the control of the bacteriophage T7 promoter encoded by prophage λ (DE3).⁶⁸⁻⁷⁰ They were subsequently isolated from inclusion bodies and purified by ion exchange chromatography.^{68,69} Both vaccines were shown to have a more than 100-fold reduced IgE reactivity and to induce protective IgG antibody responses in animals.^{68,69,71} Provocation studies in birch pollen allergic patients confirmed their reduced capacity to induce IgE-mediated allergic reactions.⁷²⁻⁷⁴ Another hypoallergenic rBet v 1 vaccine has been developed by Allergopharma. This protein consists of a folding variant of rBet v 1 (rBet v 1-FV) that was obtained using a modified procedure for purification of rBet v 1.0101 expressed in *E. coli*.^{75,76} After an initial hydrophobic interaction chromatography step at pH 8 the following three purification steps (anion exchange, hydrophobic interaction and gel filtration) were performed at alkaline pH. Recombinant Bet v 1-FV exhibited a reduced IgE reactivity and decreased capacity to activate human basophils, but had retained T cell reactivity and was strongly immunogenic, thus fulfilling the criteria for being a hypoallergen vaccine candidate.⁷⁵

A recombinant wild-type Bet v 1 is being produced for vaccine application by Stallergenes SA. The Bet v 1.0101 gene is overexpressed in *E. coli* BL21 (DE3), followed by purification of the protein in several fractionation steps including salt precipitation, affinity chromatography by hydrophobic interaction, anion exchange chromatography, several filtration steps and finally sterilisation and low-temperature storage.⁵³ The concentrated, sterile and formulated product represents GMP grade rBet v 1.0101.⁵⁴ The rBet v 1 vaccine has been subjected to a number of analyses to assess quality and characteristics of the recombinant protein

compared to purified natural (n)Bet v 1. The endotoxin content of rBet v 1 was low^{53,77} and structural analyses revealed a >99.9% homogenous monomeric protein.⁵⁴ Recently the purification method has been optimized to be able to separate the mature rBet v 1 protein from an un-cleaved N-terminal methionine Bet v 1-form, that was found as a contamination during large scale production.⁷⁸ The purified rBet v 1 was shown by circular dichroism and protein thermodynamics analyses to adopt a secondary structure closely resembling the structure of nBet v 1.^{53,54} Furthermore the immunological and allergenic properties were evaluated by ELISA/immunoblot, T-cell- and basophil activation tests.^{53,54} Recombinant Bet v 1 bound patients' IgE, stimulated proliferation of Bet v 1-specific T-cell lines and stimulated histamine release and CD203c expression on basophils from birch pollen allergic patients.

The Product of Interest

Recombinant wild-type or hypoallergenic derivatives of Bet v 1 have been applied in a couple of human allergy vaccine studies (**Table 1**). The first study employing genetically modified recombinant allergens in a clinical setting was performed with the hypoallergenic derivatives Bet v 1 fragment mix and Bet v 1 trimer^{68,69} and was sponsored by Allergopharma. In total 124 patients with allergic rhinitis and/or asthma to birch pollen were included in the double-blind placebo-controlled multi-center phase I/IIa clinical trial.⁶⁷ The three treatment groups (trimer, fragment mix and placebo) received injections with increasing doses (1–80 µg) of the substance formulated with aluminium hydroxide during a single pre-seasonal treatment period. Active treatment resulted in improvement of experienced well-being and nasal symptoms but the combined symptom-medication score did not differ significantly to the placebo group.⁷⁹ It was however clear that the hypoallergen treatment affected the Bet v 1 specific immune response. Both vaccines induced strong de novo IgG1, IgG2 and IgG4 responses to wild-type Bet v 1 and to cross reacting related pollen- and food allergens.^{67,80} Furthermore, the induced IgG4 antibodies were shown to prevent Bet v 1-mediated degranulation of basophils from birch pollen allergic patients, to reduce skin prick test reactivity and to attenuate a Bet v 1 specific IgE boost during birch pollen season in actively treated patients compared to the placebo group.^{67,81} Active treatment-induced allergen-specific IgG was found locally in nasal secretions and was associated to a reduced nasal sensitivity to Bet v 1.⁸² Also, the T-cell response to Bet v 1 was modified towards a less Th2 skewed response.⁸¹ Thus, this study implied that the hypoallergenic rBet v 1 vaccines have the capacity to modify the allergen-specific immune response and consequently have the potential to be applied as a causative treatment for birch pollen allergy.²⁰

Another rBet v 1 vaccine with reduced IgE reactivity, the rBet v 1-FV⁷⁵ developed by Allergopharma, was used to treat 24 birch pollen allergic patients in a pre-season protocol during two years.⁸³ A control group received conventional treatment with birch pollen extract. Both groups exhibited strong treatment-induced Bet v 1 specific IgG1 and IgG4 responses. In this phase II study the rBet v 1-FV treatment had a stronger effect on symptom- and

medication scores compared to the control group after the first year's treatment, but after a second pre-seasonal course of treatment the symptom-medication scores were similar for both treatment groups.⁸³ Also an additional trial including 103 placebo treated and 108 actively treated (rBet v 1-FV) patients having birch pollen allergic rhinoconjunctivitis with or without asthma (Global Initiative for Asthma, GINA, grade 1–2,⁸⁴) showed positive results.⁸⁵ The symptom medication score was significantly reduced in the rBet v 1-FV treated group compared to placebo and a larger reduction of the score was observed for actively treated patients with asthma.

A recombinant vaccine based on wild-type rBet v 1,⁵³ was evaluated in a multi-center, randomized, double-blind, placebo controlled phase II clinical trial.⁷⁷ One hundred forty-seven patients (of which 134 patients completed the study) with at least 2 years history of birch-pollen related rhinoconjunctivitis with or without mild asthma (GINA 1 or 2) were randomized into four treatment groups that underwent SCIT for two years with rBet v 1, nBet v 1,⁵³ birch pollen extract or placebo (preparations manufactured by Stallergenes SA). All patients were skin prick positive to Bet v 1 (wheal diameter >3 mm). Active treatment resulted in significant reduction in rhinoconjunctivitis symptom scores (approximately 50% improvement compared to placebo), in rescue medication scores (approx. 65% improvement) and skin reactions compared to placebo treatment. The immune response to Bet v 1 was modified in the actively treated patients; increased levels of treatment induced Bet v 1 specific IgG1, IgG4 and IgG2, but not IgE, IgA or IgG3, were found after 1–2 years treatment. Patients in the two groups vaccinated with single allergen vaccines (rBet v 1 and nBet v 1 groups) did not reveal any new or increased Bet v 2 specific IgE after the treatment in contrast to the group receiving the birch pollen vaccine in which two patients became sensitized to Bet v 2 and one patient exhibited increased IgE levels to Bet v 2. There were no significant differences in treatment-emergence adverse events reported between the four study groups. The rBet v 1 treatment was thus concluded to be safe, although a higher number of local reactions were found in the rBet v 1 treated group.⁷⁷

An rBet v 1 vaccine (Stallergenes), formulated as a dissolving tablet has been developed for SLIT application.⁸⁶ After initial Phase I studies showing that rBet v 1 tablets was tolerated at daily doses of up to 50 µg, a multicenter, randomized, double-blind, placebo-controlled Phase II trial was performed to evaluate efficacy and safety of SLIT with three rBet v 1 dose levels.⁸⁷ Four hundred eighty-three patients with birch pollen related allergic rhinoconjunctivitis were randomized into 50 µg, 25 µg, 12.5 µg or placebo treatment groups. The patients were treated daily during four months pre-season and throughout the birch pollen season. As primary end-point the Average Adjusted Symptom Score (AASS), a symptom score adjusted for rescue medication intake, and as secondary endpoint the Average Rescue Medication Score (ARMS) was recorded during the pollen season. All three actively treated groups differed significantly from the placebo group in AASS and there was no difference in efficacy between the three doses. The relative difference compared to placebo was about 20% (mean). Rescue medication intake was reported to be high

in the study but still the ARMS was approximately 33% (mean) lower for the actively treated groups, with no significant difference between the three doses, compared to placebo. The safety profile was judged to be good with generally mild to moderate and most commonly local side effects. Thus this first clinical SLIT trial with a sublingual rBet v 1 vaccine demonstrated clinically relevant efficacy in patients with birch pollen related rhinoconjunctivitis. As there was no difference in efficacy between the three active treatment doses, the lowest dose (12.5 µg) showed the best efficacy/safety profile.

Commercial and Public Health Issues

Considering the vast number of affected patients, about 20% of the population in exposed areas, birch pollen allergy is an important health problem with a significant socioeconomic impact. Currently, allergy vaccination is the only treatment that leads to long-lasting relief of symptoms. Although allergy vaccination has proven efficacious for treatment of birch pollen allergy most patients exclusively receive symptomatic treatment. In fact, medications represent the largest cost component of direct medical expenditures for asthma and rhinitis.⁸⁸ Thus it is of importance to weigh the costs for a lifelong consumption of drugs against the cost of allergy vaccination.⁸⁹ Over longer time periods it has been shown that patients treated with SCIT or SLIT vaccination display a lower mean annual cost than patients who only receive symptomatic treatment.⁹⁰⁻⁹² Therefore one can anticipate that rBet v 1 vaccines will prove cost-effective in the long run.

Conclusions

Like most allergies, birch pollen allergy is commonly treated with drugs that alleviate the symptoms but neither change the course of the disease, nor prevent progression to more severe disease. The alternative is allergy vaccination, which today is typically performed by subcutaneous injections of birch pollen extracts. As Bet v 1 is the dominant disease-eliciting allergen in birch pollen, the development of single component birch pollen allergy vaccines

composed of rBet v 1 or rBet v 1 derivatives is promising. These vaccines are easier to standardize compared to allergen extracts and allow engineering to create improved allergy vaccines. One rationale for employing genetically engineered hypoallergenic rBet v 1 vaccines is that higher treatment doses of the rBet v 1 derivatives should be tolerated. Due to the study design the clinical trials performed with rBet v 1 hypoallergen vaccines so far have not generated data able to demonstrate that rBet v 1 derivatives are more efficient than the natural extract. Studies directly comparing rBet v 1 hypoallergen vaccines to rBet v 1/nBet v 1 are needed and the protocols for vaccination with hypoallergenic vaccines need to be optimized. The results obtained so far from clinical trials with the rBet v 1 vaccine have demonstrated positive effects. A phase II SCIT study comparing the rBet v 1 vaccine to natural Bet v 1 and birch pollen extract vaccines showed similar efficacy and safety for the three vaccines. The first clinical trial of a recombinant allergen SLIT tablet, the sublingual rBet v 1 vaccine, demonstrated clinical efficacy indicating that SLIT with rBet v 1 will potentially become a significant treatment option for birch pollen allergic patients. However, some of the obstacles experienced with allergen extract vaccines (e.g., long treatment periods and risk of adverse effects) still remain to be solved for the rBet v 1 vaccines. Hopefully the availability of GMP produced rBet v 1 will facilitate the continued development of improved rBet v 1 vaccine formulations. Such improvements may e.g., be achieved by formulating rBet v 1 with adjuvants or immunomodulating agents.⁹³⁻⁹⁹ Vaccines designed for new delivery routes, e.g., for intralymphatic or epicutaneous administration, also constitute an interesting exploitation option.^{100,101} The cost and convenience for the patients has to be taken into account when designing novel vaccines for treatment of birch pollen allergy. In a future perspective prophylactic allergy vaccines similar to vaccines used for infectious diseases should be considered. For such purpose an rBet v 1 vaccine could be combined with other common allergy component vaccines. A prophylactic allergy vaccine may be given to children at high risk to develop allergic disease in order to induce a properly regulated non-IgE response i.e., allergen tolerance, to the allergens.

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