review

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Allergen immunotherapy for oral allergy syndrome: what is the evidence for efficacy?

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Abstract
Background The vast majority of IgE-mediated food allergies in adults are based on sensitization to pollen and subsequent cross-reactions to structurally related allergens in fruit, vegetables, and spices. The effect of allergen immunotherapy (AIT) against pollen on pollen-related food allergy has not been conclusively elucidated.
Methods A review of studies on AIT in pollen-related food allergy was conducted.
Results The fact that the published studies show considerable differences in terms of design (e.g., number of subjects, treatment duration, mode of administration, allergen content, oral provocation testing) hampers their evaluation and comparison. Only some of the studies demonstrated an improvement in pollen-related food allergy as a result of AIT with pollen allergens.
Conclusion Reliable recommendations on the use of AIT with pollen allergens in pollen-related food allergy are not possible as yet. AIT with birch pollen allergens appears to have a positive effect on concomitant food allergy in some patients with birch pollen allergy.

Keywords Food allergy · Therapy · Birch · Pollen · Review

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Abbreviations

AIT	Allergen immunotherapy
BASALIT	Birch-related soy allergy and immunotherapy
DBPCFC	Double-blind placebo-controlled food challenge
FA	Food allergy
FAQLQ-AF	Food Allergy Quality of Life Questionnaire-Adult Form
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
ISAC	Immuno solid-phase allergen chip
LOAEL	Lowest observed adverse effect level
OAS	Oral allergy syndrome
OPT	Oral provocation testing
sIgE	Specific immunoglobulin E
SPT	Skin prick test

Introduction

The majority of IgE-mediated food allergies in adults are based on sensitization to aeroallergens (in particular pollen) with subsequent reactions (cross-reactions) to structurally related, often unstable allergens, particularly in fruit, vegetables, and spices. This type of food allergy is referred to as a secondary food allergy, as distinct from the primary form, which is presumed to involve sensitization via the gastrointestinal tract [1–4]. Birch pollen-related food allergies are by far the most prevalent in Germany.

Symptoms of pollen-related food allergy typically manifest within a few minutes to up to 2 h following intake of the food. Oropharyngeal contact urticaria (also referred to as oral allergy syndrome, OAS) occurs most commonly. Reactions may also be seen in one or more target organs, including the skin, gastrointesti-

nal tract, respiratory tract, and cardiovascular system [1].

In terms of treatment, and in addition to allergen avoidance, (emergency) anti-allergic drugs are used where required. In contrast to pollen-related respiratory symptoms, there are controversial data on whether allergen immunotherapy (AIT) has a positive effect on pollen-related food allergy [2, 5, 6]. AIT has been attempted with the food allergens themselves, as well as with the associated pollen allergen.

The following review presents the current state of knowledge on the performance of AIT with pollen extracts for pollen-related food allergy, with particular attention to birch-related food allergy.

Triggers of birch-related food allergy

The main plant-based food allergens belong to a handful of protein families: the best known of these are Bet v 1 homologues, lipid transfer proteins, storage proteins, and thaumatin-like proteins [1].

Bet v 1 homologues are widespread in the plant world, and hence also in fruit and vegetables. The types of fruit that are most frequently involved in pollen-related food allergy belong to the Rosaceae (e.g., apple, cherry) and Fagales families (hazelnut). In terms of vegetables, celery and carrot from the Apiaceae family, as well as tomato and bell pepper, are particularly worthy of note ([1]; Table 1). In a Bet v 1-sensitized patient group ($n=221$) that was investigated for specific IgE to PR10 proteins using immuno solid-phase allergen chip (ISAC), concomitant sensitization was detected to Cor a 1.04 (98%), Mal d 1 (94%), Aln g 1 (94%), Pru p 1 (86%), Cor a 1.01, Ara h 8 (72%), Gly m 4 (52%), Api g 1 (37%), and Act d 8 (29%) [7].

Allergen immunotherapy and extracts

AIT is a causal immunomodulatory treatment aimed at inducing immune tolerance through the administration of allergen extracts. The effect is triggered by specific blocking antibodies, tolerance-inducing cells, and messengers, which prevent further exacerbation of the allergen-triggered immune response, block the specific immune response, and attenuate the inflammatory response in tissue.

The guidelines [5] specify that the following criteria should be met in order for AIT to be initiated:

- Detection of IgE-mediated sensitization (preferably using skin tests and/or in vitro diagnostic methods) and an unequivocal link to clinical symptoms (provocation testing where appropriate)
- Availability of standardized or high-quality allergen extracts
- Proof of efficacy of the planned AIT for the respective indication and age group
- Allergen avoidance not possible or inadequate

Subcutaneous or sublingual products are available for immunotherapy. Native foods, allergen extracts, and allergen peptides have been used in studies on patients with food allergy to, e.g., cow's milk, hen's egg, and peanut, either subcutaneously, sublingually, orally (selective oral tolerance induction), or epicutaneously [6].

Biomarkers

In vitro and in vivo biomarkers can be used to establish the indication for AIT; some of these are also suited to monitoring disease course or treatment success [5, 6, 8]. It is not possible to say with any certainty at present the extent to which the serological markers used in inhalant pollen allergy, as well as skin prick tests (SPT), are suited to the evaluation of AIT course and success in pollen-related food allergy.

In vitro markers

In order for AIT to be indicated, IgE-mediated sensitization needs to be proven, e.g., by specific serum IgE. Molecular allergy diagnostics have made such significant advances here in recent years that, in addition to Bet v 1 sensitization, IgE antibodies to a number of cross-reactive food allergens can be detected, e.g., to Mal d 1 (apple), Cor a 1 (hazelnut), and Gly m 4 (soy) [9–12]. It was recently shown that those with concomitant OAS in a birch-allergic patient group had higher levels of specific immunoglobulin E (sIgE) to Bet v 1 compared with those without concomitant pollen-related food allergy [9]. Another working group, on the other hand, found no association between IgE, IgG4, or IgA to Bet v 1 and the clinical onset of OAS [13]. Specific IgG4 determination is generally performed to evaluate the extent to which an immunological response takes place under AIT, although no clinically relevant success can be inferred from this.

Skin testing

SPT can be used to diagnose an IgE-mediated reaction. However, according to the current state of knowledge, there is no evidence to suggest that SPT can be used to evaluate the success of AIT for pollen-related food allergy.

Oral provocation testing

Older studies on AIT for pollen-related food allergy refer exclusively to information from patients in the context of non-controlled consumption in terms of food-related symptoms. Meanwhile, double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard; however, this test is by no means straightforward. Overall, DBPCFC is still in great need of standardization [14]. This applies to:

Table 1 Bet v 1-homologues food allergens[a] (www.allergome.de) [1]

Family	Allergen	Biochemical name	Source
Fagales	**Cor a 1**	*Corylus avellana*	Hazel(nut)
	Cas s 1	*Castanea sativa*	Chestnut
Rosaceae	**Mal d 1**	*Malus domestica*	Apple
	Pyr c 1	*Pyrus communis*	Pear
	Pru p 1	*Prunus persica*	Peach
	Pru av 1	*Prunus avium*	Wild cherry
	Pru ar 1	*Prunus armeniacae*	Apricot
	Fra a 1	*Fragaria ananassa*	Strawberry
Legumes	**Ara h 8**	*Arachis hypogaea*	Peanut
	Gly m 4	*Glycine maximus*	Soybean
	Vig r 1	*Vigna radiata*	Mung bean
Apiaceae	**Api g 1**	*Apium graveolens*	Celery
	Dau c 1	*Daucus carota*	Carrot
	Pet c PR-10	*Petroselinum crispum*	Parsley
	Foe v 1	*Foeniculum vulgare*	Fennel
	Cor s 1	*Coriandrum sativum*	Coriander
	Cum c 1	*Cuminum cyminum*	Cumin
	Pim a 1	*Pimpinella anisum*	Anise
Compositae	Mat c 17 kD	*Matricaria chamomilla*	Chamomile
	Tar o 18 kD	*Taraxacum officinale*	Dandelion
Liliaceae	Aspa o PR protein	*Asparagus officinalis*	Asparagus
Solanaceae	Cap a 17 kD	*Capsicum annuum*	Bell pepper
	Cap ch 17 kD	*Capsicum chinense*	Chilli pepper
Ebenaceae	Dio k 17 kD	*Diospyros kaki*	Persimmon
Anacardiaceae	Man i 14 kD	*Mangifera indica*	Mango
Papaveraceae	Pap s 17 kD	*Papaver somniferum*	Opium poppy
Actinidiaceae	**Act d 8**	*Actinidia deliciosa*	Kiwi
Juglandaceae	Jug a 5	*Juglans regia*	Walnut

kD kilodalton
[a]Allergens in bold can be commercially determined

- Timing (e.g., stronger reactions during the pollen season)
- Provocation meals (e.g., allergen selection/administration, allergen dose, allergen content, blinding, placebo meal)
  Due to a lack of commercial availability to date, there has been no standardization in terms of allergen content. When using native foodstuffs, allergen content may differ as a result of, e.g., variety, as well as growing and storage conditions. An attempt was made to counter this situation in soy allergy by using standardized Gly m 4 measurements [15]. There are also preliminary studies in which the major apple allergen, Mal d 1, was used for oral challenge testing [16, 17].
- Dose escalation schedule (e.g., every 20–30 min) [18]
- Evaluation criteria and determining the final value (e.g., shifting the threshold value following AIT) [18].

Threshold values are set using the lowest observable adverse event level (LOAEL), defined as the lowest dose of the food at which symptoms or clinical signs manifest. Studies only rarely provide detailed information on the DBPCFC evaluation criteria used. Unfortunately, there is no consensus-based standard as yet on to how objective signs and subjective symptoms can be measured and evaluated. The evaluation of placebo reactions, which are not uncommon, also presents a challenge [14, 18].

Measuring quality of life

The Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) is the first freely available questionnaire designed to measure health-related quality of life in adults with food allergy. It was recently shown in an adult patient collective with exclusively pollen-related food allergy that the questionnaire can also be used for this entity. It was reported that OAS impairs quality of life to the same extent as food allergy symptoms that go beyond OAS [19].

Table 2 Studies on the use of allergen-specific immunotherapy in birch-related food allergy

Author/year	Food allergy	Administration	*n*	Extract (manufacturer)	Control Pl/nT *n*	Treatment duration (months)	OPT	Threshold dose determination	Principal effect described
Asero 1998 [22]	A	SC	33	Allergopharma retard birch Alhydrox birch (Bayer)	26 (nT)	12–36	Open	No	Clinical improvement in 41/49 (84%) under AIT vs. 0/26 of nT controls
		SC	16						
Bolhaar 2004 [23]	A	SC	25	Alutard birch (ALK-Abello)	12 (nT)	12	DBPC	Yes	Clinical improvement in 9/13 (69%) under AIT vs. 0/12 (Pl)
Bucher 2004 [24]	A H	SC	15	Alutard TP/EB mix (sometimes with ash, ALK-Abello)	12 (nT)	5–36	Open	Yes	Clinical improvement in 13/15 (87%) under AIT vs. 1/12 (8%) of Pl controls
Hansen 2004 [25]	H	SL	12	Staloral birch (Stallergenes) Phostal birch (Stallergenes)	14 (Pl)	24	Open	No	No significant change in threshold dose/symptoms; increase in IgG4 for Cor a 1
		SC	16						
Kinaycian 2007 [26]	A	SL	15	Pangramin (ALK-Abello)	n.p.	12	DBPC	No	No significant clinical change No significant change IgG4 for apple
Mauro 2011 [27]	A	SC	24	Staloral EB mix (Stallergenes) Staloral EB mix (Stallergenes)	n.p.	12	Open control OPT, *n* = 15	Yes	Clinical improvement in 5/8 (SCIT) Clinical improvement in 3/7 (SLIT)
		SL	23						
v Hoffen 2011 [28]	H	SC	10	Alutard birch (ALK-Abello)	9 (Pl)	12	DBPC	Yes	No significant clinical change IgG4 increase for Bet v 1, Cor a 1
Geroldinger-Simic 2013 [29]	A	SL	18	GMP-rMal d 1	n.p.	2 Days	n.p.	–	Drop in sIgE Mal d 1 and IL-5 and IL-10 induction
Subbarayal 2013 [20]	A, H	SC	42	ALK depot birch or ALK depot EB (ALK-Abello)	n.p.	30–36	n.p.	–	IgG4 Mal d 1, IgG4 Cor a 1 increase, sIgG4 inhibits sIgE binding, basophil activation, and T-cell proliferation
Treudler 2017 [1]	S	SC	56	rBet v 1 FV (Allergopharma)	18 (Pl)	12	DBPC	Yes	Improved threshold dose for objective signs (trend), IgG4 increase for Gly m 4
Kinaycian 2018 [31]	A	SL	60	Bet v 1 (Biomay) Mal d 1 (Biomay)	20 (Pl)	4	Open	Yes	Improved threshold dose only Mal d 1 group

Pl placebo, *nT* no treatment, *OPT* oral provocation testing, *A* apple, *H* hazel, *S* soy, *TP* tree pollen, *EB* early bloomer, *FV* folded variant, *SC* subcutaneous, *SL* sublingual, *GMP* good manufacturing practice, *DBPC* double-blind placebo-controlled, *n.p.* not performed, *SCIT* subcutaneous immunotherapy, *SLIT* sublingual immunotherapy

Data on allergen-specific immunotherapy for pollen-related food allergy

AIT with birch pollen extracts causes the induction of Bet v 1-specific (s)IgG4 antibodies. There has been discussion that these sIgG4 antibodies cross-react with related food allergens, e.g., Mal d 1 and Cor a 1, thereby inhibiting the IgE binding of these allergens. This inhibitory effect could be measured as early on as 1 year following AIT and further increased after 3 years (cumulative allergen dose 500 µg). A reduction in sIgE antibodies to food allergens was also demonstrated, albeit only after 12 months of AIT. Interestingly, IgG4 antibodies in this investigation failed to recognize more than 35% of epitopes of Bet v 1, Mal d 1, and Cor a 1, meaning that the sIgG4 induced by AIT apparently does not cover or prevent all IgE activities [20].

However, based on the available in vitro data, one can indeed expect AIT with birch pollen extracts to have a clinical effect on birch-related food allergy [21].

When evaluating the existing studies (Table 1), one must bear in mind that there are significant differences in study design [14, 22], particularly in terms of:

- Extracts with varying allergen contents used
- Mode of administration (sublingual, subcutaneous)
- Group size (mostly extremely small groups, probably statistically underpowered)
- Food allergens investigated (hazelnut, apple, soy)
- Performance and evaluation of provocation testing

This makes a comparison virtually impossible. Only a handful of studies included a placebo-controlled intervention, while others chose a treatment-free control group to determine treatment effect (Table 2; [22–30]). The double-blind food challenge with threshold value determination, defined as the gold standard [2], was fulfilled in only some of the studies.

Overall, a number of studies did indeed yield evidence that AIT with pollen allergens has a clinical effect on birch-related food allergy. It is possible that even better effects can be achieved by using molecular food allergens (e.g., Mal d 1) in allergen extracts, as recently shown in a study on birch-related apple allergy [31].

The lack of AIT's clinical effect in other studies has been linked, first, to an overly low number of cases and, second, to the different pollen allergen extracts used. Thus, it was speculated that in order to achieve a positive effect on pollen-related food allergy the allergen dose used would need to be higher than the dose usually used in pollen-induced respiratory symptoms (in particular allergic rhinoconjunctivitis) [32]. For the most part, allergen extracts with 12.5–25 µg of major allergen were used to investigate the effect of AIT on birch-related food allergy (Table 2). Whether a high-dose extract with 80 µg of folded recombinant Bet v 1 is more successful in birch-related food allergy was investigated in a randomized placebo-controlled multicenter study using birch-related soy allergy as an example (birch-related soy allergy and immunotherapy/BASALIT study) [20, 30, 33, 34].

In general, the multicenter BASALIT study [30] is characterized by:

- Randomized placebo-controlled study both in terms of diagnosis using oral food challenge [14] and treatment
- The use of high-dose (80 µg) Bet v 1 extract for subcutaneous AIT
- The use of a standardized challenge meal with controlled Gly m 4 allergen content [15]
- Standardized criteria to evaluate subjective symptoms and objective signs [14]
- A high number of subjects compared with previous studies: 82 patients tested positive in oral provocation testing (OPT) to soy, 56 of which were randomized to interventional placebo-controlled AIT (verum–placebo ratio: 2:1)

The BASALIT study showed that 1-year AIT has a clear immunological effect on sIgG4 antibody production to Bet v 1. A significant increase in sIgG4 antibodies to Gly m 4 and Cor a 1 was also documented.

In terms of clinical effect, the verum group showed an improvement in the threshold dose for objective signs (LOAEL), with post-interventional reactions to the challenge meal only occurring at higher doses compared with the baseline investigation. However, what was remarkable was that similar improvements in LOAEL were also observed in some of the subjects in the placebo group. It is unfortunate, therefore, that statistical significance was not achieved for this effect ($p = 0.08$), which—despite the comparatively high number of subjects included—was attributed to the fact that only 56% of the sample size calculated as necessary for a clearly demonstrable effect could be recruited [30]. The BASALIT study demonstrates the difficulty associated with conducting studies to investigate the effect of AIT in pollen-related food allergy.

Outlook

A recent study showed, both in vitro and in a mouse model, that vaccination with a hybrid molecule directed against the three relevant T-cell epitopes, Bet v 1, as well as cross-reactive apple and hazelnut epitopes, is capable of inducing protective antibodies in pollen-related food allergy [35]. It is possible that synthetically produced immuno-regulatory peptides could be used in the context of AIT in the future [36]. Another potential treatment option for food allergy may be the use of the anti-IgE antibody omalizumab, for which the first cases of treatment success have been shown, either alone or in combination with oral immunotherapy [37, 38].

Summary: what is the evidence for efficacy?

It is important to note that, on the whole, knowledge regarding the use of AIT in pollen-related food allergy has been limited to date. This is due to the fact that there are only scant randomized placebo-controlled treatment studies that conducted their investigations using defined AIT extracts. To complicate matters further, there are no standardized target parameters for the evaluation of food allergy severity that are suited to measuring the extent of symptoms before and after AIT. Finally, there are no readily available, standardized challenge meals for which a defined allergen content can be assumed. Therefore, all things considered, one must currently assume an evidence level of 1b (at least one sufficiently large, methodologically high-quality randomized study) to 2a (at least one high-quality study without randomization), since even recent high-quality studies were unable to recruit a sufficient number of patients [29]. As such, the grade of recommendation that can currently be given is essentially only level B (findings based on reliable level-2 or level-3 studies or on extrapolations from level-1 studies) and does not reach level A (findings based on reliable level-1 studies).

In summary, one would have to say that AIT with Bet v 1 that is successful in terms of respiratory symptoms does not necessarily improve pollen-related food allergy. However, it certainly appears to have positive effects on concomitant food allergies in some patients. One can assume that precise criteria are still lacking on which subgroup of Bet v 1-sensitized individuals would in actual fact also benefit in terms of pollen-related food allergy. The evidence to date does not permit pollen-related food allergy alone to be considered an indication for AIT. Therefore, in accordance with the guidelines, AIT with pollen allergens should only be performed if the indication is made on the basis of concomitant respiratory symptoms [2].

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