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Rapid dose escalation with monomeric tree pollen allergoid drops is well tolerated in patients with allergic rhinoconjunctivitis and points towards clinical effects

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Introduction

Pollen allergy is currently affecting about 40% of all allergic patients in Europe and the prevalence is increasing, with birch (Betula) being the most common tree pollen allergen. Carbamylated monomeric allergoids play a special role in the treatment of pollen allergies for their lower allergenic potential and lower susceptibility to enzymatic degradation.

Aim of this investigation was to identify a safe maximal dose range for once-daily administration up to 50,000 UA of sublingual drops in patients with allergic rhinoconjunctivitis.

Methods

A randomized, double-blind, placebo-controlled trial was conducted in 21 patients in 5 centres in Germany.

Safety and clinical tolerability were assessed, inter alia, by means of solicited (expected) local (according to Passalacqua et al.) and unsolicited (unexpected) adverse drug reactions (ADRs), as well as systemic reactions according to Ring et al. The severity of ADRs were either rated as mild, moderate or severe.

The clinical impact was analysed by conjunctival allergen provocation testing (CPT) by means of CPT reactivity and composite score before and after treatment. Changes in immunological status were analysed by measuring Bet v1 specific IgE and IgG4 at V1 and V6.

Day	Visit	Dose of tree pollen drops [UA]	Dose of placebo [UA]
1	V2[a]	2,000	0
		5,000	0
		10,000	0
2 to 3	h[b]	10,000	0
4	V3[a]	15,000	0
		25,000	0
5 to 7	h[b]	25,000	0
8	V4[a]	50,000	0
9 to 71	m[b]	50,000	0

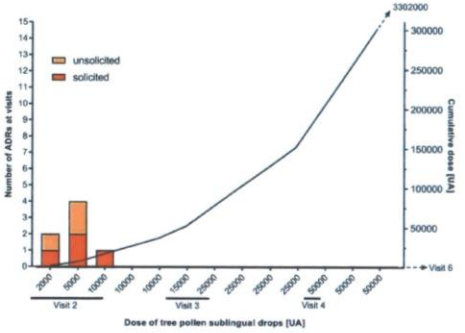
[a]: administration at doctor's office, [b]: self-administration by the patient at home

Methods

Treatment Schedule

Updosing was performed before the birch pollen season 2018 in 3 visits (V2-V4) within 8 days. Doses increased from 2,000 UA to 50, 000 UA in 5 steps. The individual maximum tolerated daily dose was maintained for another 62 days. In between, a control visit (V5) was performed. After 71 days an end of treatment visit (V6) was done.

h: home interphase between updosing visits; m: maintenance phase after updosing; UA: Units of Allergen; V: Visit



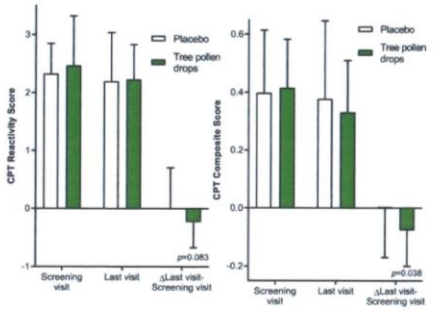
Results

Tolerability

Number of ADRs (adverse reactions) after administration of tree pollen sublingual drops in the doctor's office.

A total of seven ADRs occurred in two patients: four solicited (itching of lips, throat irritation according to Passalacqua et al.) and three un-solicited (MedDRA PT: administration site hypersensitivity, administration site irritation). One patient experienced three ADRs (two at 2,000 and one at 5,000 UA) and the other patient experienced four ADRs (three at 5,000 and one at 10,000 UA).

UA: Units of Allergen



Results

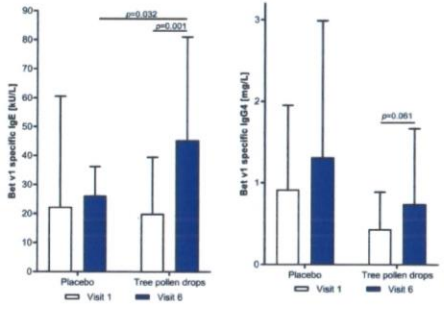
Clinical effects

CPT reactivity score (left) and CPT composite score (right) before (at screening visit) and after treatment (last visit, V6 or V6b).

CPT reactivity was reduced by 5.6% in the placebo and by 9.7% the actively treated group from screening to last visit.

During the study, the composite score decreased by 7.5% in the placebo patients. In the actively treated patients, the score was significantly reduced by 19.5% (p=0.038).

Data is expressed as mean + SD. p<0.05 was considered as being significant.



Results

Immunologic parameters

Birch pollen specific IgE (sIgE, left) and IgG4 (sIgG4, right) at V1 and V6.

In the placebo group, sIgE was elevated by 17% at V6 compared to V1. In the actively treated group, sIgE showed a 1.7-fold increase (p=0.001) from V1 to V6. At V6, sIgE of actively treated patients was 1.7-fold higher than in placebo patients (p=0.032).

sIgG4 increased 1.4-fold and 1.7-fold in the placebo and the actively treated, group, respectively.

Data is expressed as mean + SD. p<0.05 was considered as being significant

kU: kilo Units; L: Litre; mg: milligram

Results

Of the 21 patients, 6 were allocated to the placebo and 15 to the actively treated group. Over 90% of the patients (6 placebo and 13 actively treated patients) completed the trial (median treatment duration: 68 days). Overall, no fatality, no severe nor serious ADRs occurred during the trial. No epinephrine was used. The intended cumulative dose of 3,302,00 UA ± 30% was received by more than 85% of the actively treated patients. During treatment, one patient experienced systemic allergic ADRs (grade I, mild rhinitis) and was withdrawn from the trial. No systemic ADR grade II or higher occurred. Solicited and unsolicited ADRs occurred in 1.1% of all doses (920 doses in total) and only during updosing. Their severity was mild and no dose adjustment was necessary. No ADR occurred during the maintenance phase from V4 to V6. One patient discontinued the trial because of unrelated worsening of seasonal allergic symptoms, because of increased pollen flight at the onset of the season.

Conclusion

This early phase clinical dose escalation study has successfully demonstrated the safety and the feasibility of this high dose concept of sublingual allergen immuno-therapy with the carbamylated allergoid.