

Tolerability of a New Fast Updosed Immunologically Enhanced Subcutaneous Immunotherapy Formulation With an Optimized Allergen to Adjuvant Ratio Under Routine Practice Conditions: A Noninterventional Observational Study

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■ Abstract

Background and objectives: A fast updosed immunologically enhanced subcutaneous immunotherapy (SCIT) formulation with an optimized allergen to aluminium hydroxide ratio was first introduced in September 2009 in Germany. A large randomized controlled trial showed that the formulation had considerable immunologic effects and good tolerability. In this open-label, uncontrolled, noninterventional study, tolerability was investigated during routine application.

Patients and methods: Patients with allergic rhinoconjunctivitis and/or asthma were treated with pollen and mite allergens using a 5-injection updosing schedule (AVANZ: 300, 600, 3000, 6000 and 15 000 SQ+ units) with weekly intervals, followed by a maintenance schedule with injections of 15 000 SQ+ units. Adverse events (AEs) were recorded by physicians, and symptoms and use of symptomatic medication were analyzed before the start of therapy and after an average 8-month treatment period.

Results: SCIT was documented by 362 allergists in 1036 patients between September 2009 and February 2011. AEs mainly consisted of local reactions during updosing (in 24.5% of patients). Systemic reactions were observed during updosing (8.4%) and maintenance therapy (1.7%), the most frequent of which was dyspnea. Overall, tolerability and the effect of treatment were rated as good or very good by 94.9% and 86.6% of patients and by 96.2% and 89.6% of physicians, respectively.

Conclusions: In this open-label, noninterventional study, fast updosed immunologically enhanced SCIT (AVANZ) was well tolerated in a large group of patients.

Key words: Adjuvant. Immunomodulators. Immunology. Short updosing. Subcutaneous immunotherapy. Tolerability.

■ Resumen

Antecedentes y objetivos: En septiembre del 2009 fue introducida en Alemania una nueva formulación de inmunoterapia subcutánea (SCIT), de inicio rápido, con una relación de alérgeno /hidróxido de aluminio optimizada para mejorar su actividad. Sus efectos sobre el sistema inmune y su adecuada tolerancia han sido bien establecidos mediante un gran estudio controlado y aleatorizado. Mediante un estudio abierto, no controlado, de práctica en vida real, se ha estudiado la tolerancia de esta nueva inmunoterapia.

Pacientes y Métodos: Se seleccionaron pacientes diagnosticados de rinoconjuntivitis alérgica con o sin asma, siendo tratados con extracto de pólenes o ácaros, siguiendo una pauta de inicio rápida en 5 administraciones (AVANZ®: 300, 600, 3000, 6000 and 15000 unidades SQ+) en intervalos semanales, seguidos de un mantenimiento de 15 000 unidades SQ+. Los médicos participantes registraron los efectos adversos del tratamiento (AEs) y también se registraron el consumo de medicación de rescate y la sintomatología, antes de iniciar el tratamiento y tras un periodo medio de tratamiento de 8 meses.

Resultados: En el estudio participaron 362 alergólogos y 1036 pacientes que realizaron los registros entre septiembre del 2009 y febrero del 2011. Se observó algún efecto adverso, predominantemente reacciones locales, en el 24,5% de los pacientes. Con respecto a los efectos adversos sistémicos, ocurrieron en el 8,4% de los pacientes en el periodo de inicio, y en un 1,7% de los pacientes en el periodo de mantenimiento. El efecto sistémico más frecuente fue la disnea. En conjunto, la tolerancia fue calificada como buena o muy buena por el 94,9% de los pacientes y el 96,2% de los médicos. En el mismo sentido calificaron el efecto del tratamiento el 86,6% y 89,6% respectivo. **Conclusiones:** Este estudio en vida real, abierto y no controlado, realizado en un gran número de pacientes, confirma que la inmunoterapia optimizada y rápida AVANZ tiene una buena tolerancia.

Palabras clave: Adjuvante. Inmunomoduladores. Inmunología. Inicio rápido. Inmunoterapia subcutánea. Tolerancia.

Introduction

The prevalence of allergic diseases, including allergic rhinitis and asthma, has been increasing over the last 2 decades [1].

Specific immunotherapy (SIT) is the only treatment modality capable of influencing the natural course of allergic disease, at best preventing progression [2]. It has the potential to halt progression from rhinitis to asthma, at least in the case of products containing intact allergens combined with aluminium hydroxide [3]. Treatment involves repeated administrations of specific allergen extracts with the aim of inducing immunologic tolerance and reducing symptoms on subsequent natural allergen exposure to achieve a long-term treatment effect and improve quality of life [4].

The clinical effectiveness of subcutaneous immunotherapy (SCIT) is well established and has been demonstrated in a meta-analysis [5]. However, the long up dosing phases necessary in conventional SCIT with intact nonmodified allergens over a period of several weeks can make treatment inconvenient for patients, as well as for centers with large numbers of patients [6].

Aluminium hydroxide, which is widely used in SCIT for slow allergen release, has also been identified as an adjuvant. The mode of action is still not completely understood but it may be effective through danger signals via activation of the NLRP3 inflammasome complex [7-10].

To improve the convenience of SCIT, a new fast up dosed immunologically enhanced SCIT formulation (AVANZ) with an optimized allergen to aluminium hydroxide ratio was developed to allow for the administration of lower doses and thus shorter up dosing schedules while maintaining the immunogenicity compared to traditional SCIT. The maintenance dose of this formulation is reduced to 15 000 SQ+ units compared to the recommended maximum maintenance dose of 100 000 SQ units with traditional SCIT (Alutard SQ); concentrations of aluminium hydroxide and other excipients are kept at the same level [6].

The immunologic efficacy of the new fast up dosed immunologically enhanced SCIT formulation was demonstrated to be equivalent to traditional SCIT [6,11]. It became available as a Named Patient Product for routine use in Germany in 2009, in Italy in 2010, and in Spain and Austria in 2011.

Systematically recorded data on the application and tolerability of the new formulation in real life, however, are needed to evaluate the risks and benefits of the new product in daily use.

The objective of the present observational study was to systematically record data on tolerability of the new SCIT product for a large group of patients treated with pollen and mite allergens under routine practice conditions.

Patients and Methods

In this multicenter, open-label, noninterventional observational study, we recorded up dosing with 5 injections of an immunologically enhanced allergen product and subsequent maintenance injections for a total treatment period of up to 1 year. The main study visits were performed at the start of up dosing and at the end of the observation period.

The centers participating in this study were distributed evenly across Germany. For this purpose allergists applying SIT were registered in regional lists and asked to participate in the study following random rearrangement of the list. Each center was asked to record data for 3 consecutively recruited patients who agreed to participate in the study. Together, the random selection of the centers and the consecutive enrolment of study patients represent a suitable measure to avoid selection bias in the study population. Physicians were asked to note down all patients who were potentially eligible for the study in a patient's log to ensure the selection process remained fully transparent.

The study was conducted in 362 allergy centers in Germany between September 2009 and February 2011 and included 1036 patients with type I allergies caused by various pollen allergens or mites; most of the patients had allergic rhinoconjunctivitis with or without asthma. All the patients with a type I allergy mediated by pollen allergens or mites and an indication for SIT for whom the decision to apply SCIT with the immunologically enhanced formulation (AVANZ) had been taken independently of the study were eligible for documentation in the study.

At inclusion, the physicians recorded each patient's allergy history, with inclusion of the following information: age at first onset of allergic complaints, age when the allergy was first diagnosed, clinical manifestations of the allergy (rhinitis/conjunctivitis/bronchial asthma/atopic dermatitis/other, if applicable), concomitant allergies, previous courses with SIT, and the diagnostics applied for the allergen treated by SCIT. Symptoms and medication use in the previous season or previous period before SCIT was started were assessed retrospectively. Symptoms affecting the nose, eyes, and bronchi were graded as absent/mild (transient symptoms,

no interference with the patient's daily activities), moderate (marked symptoms, mild interference), or severe (considerable symptoms, unacceptable interference). Use of concomitant symptomatic medication was classified as no medication, topical or oral antihistamines, topical, oral, or inhaled corticosteroids, inhaled β -sympathomimetics, or other.

At the final visit overall tolerability (very good, good, moderate, or poor) and continuation of treatment beyond the end of the observation period were assessed.

Patients were treated with birch, tree mix, grass mix and rye, mite mix, timothy, or mugwort allergens (Table 1). The prescription and the use of AVANZ were subject to individual treatment needs at the discretion of the physician. Allergen extracts were standardized by ALK according to internal standards; the biological activity was determined as previously described [13,14] and expressed in immunologically enhanced standardized quality (SQ+) units. SCIT was initiated using a 5-step updosing schedule (300, 600, 3000, 6000, 15 000 SQ+) at injection intervals of 1 week. Updosing was followed by maintenance treatment with 15 000 SQ+; the first dose was administered after 2 weeks and thereafter at intervals of 6 \pm 2 weeks.

Data were recorded during regular visits to the clinic. For each injection the dose and the applied volume were recorded and a note was made of whether anti-allergic premedication had been used prior to injection.

For assessment of tolerability, all adverse events (AEs) were collected and recorded according to diagnosis or description, time of onset postinjection, duration, severity, causality with injection, medical measures taken, outcome, seriousness, and discontinuation, if applicable. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). They included local and systemic reactions, other AEs not attributable to single injections, and serious AEs (SAEs). Adverse drug reactions were defined as either immediate (occurring 0-30 minutes after injection) or delayed (occurring >30 minutes after injection).

An AE was assessed as severe when the event considerably interfered with the patient's daily activities. A serious AE was defined as any medical occurrence or effect that was life-threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity, resulted in death, congenital abnormalities, or birth defects, or any other event judged medically important.

Statistical Analysis

Statistical analyses were performed using SAS software, versions 8.2, 9.1.3, and 9.2 (SAS Institute). Data were analyzed by descriptive statistical methods using minimum, maximum, median, mean and SD for continuous data as well as frequency distributions for ordinal data. AEs were displayed for patients and for the frequency of events including multiple occurrences by patient. The sample size was planned to be at least 900 in order to detect adverse drug reactions of low incidence (0.5%) with high probability (99%) at least once. We therefore aimed to include at least 300 physicians, each recording data for 3 patients, in the study. The All-Patients-Treated set was stratified with respect to the allergen used, especially birch, tree mix, grass mix and rye, and mite mix.

Results

Patients

Data for 1036 patients treated with 1 of the allergens—birch, tree mix, grass mix, mite mix, timothy grass, or mugwort (see Figure 1)—were evaluated with respect to tolerability for the up dosing phase of treatment; 947 patients continued with the maintenance treatment. The average duration of treatment was 225 days with a median of 11.0 injections. The patients' characteristics are shown in Table 1.

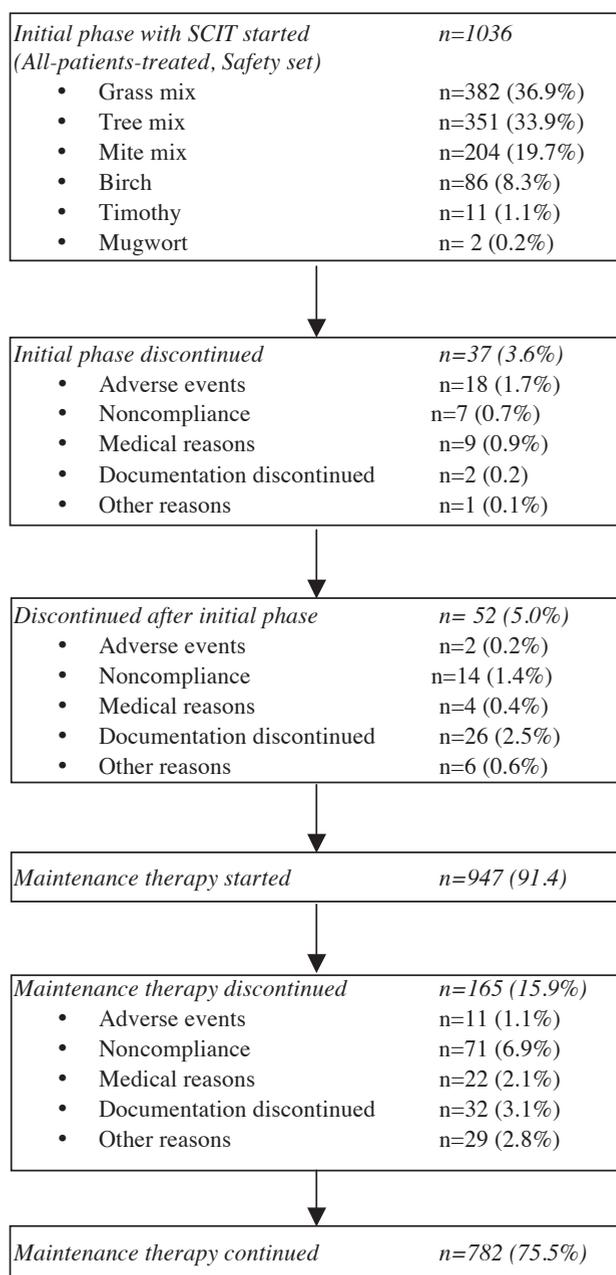


Figure 1. Flow of patients through the study. SCIT indicates subcutaneous immunotherapy.

Table 1. Patient Characteristics

	Birch	Tree mix	Grass mix	Mite mix	All patients
Patients, No.	86	351	382	204	1036 ^a
Age, median (range), y	36.5 (9-67)	40.0 (10-72)	33.0 (9-79)	29.5 (7-80)	36.0 (7-80)
Sex, No. (%)					
Male	39 (45.3)	171 (48.7)	191 (50.0)	93 (45.6)	501 (48.4)
Female	47 (54.7)	180 (51.3)	191 (50.0)	111 (54.4)	535 (51.6)
BMI, mean (SD), kg/m ²	25.2 (5.2)	24.8 (3.8)	24.6 (4.0)	24.0 (3.4)	24.6 (4.0)
Duration since diagnosis of the pollen/mite allergy, mean (SD), y	5.9 (7.7)	7.5 (9.5)	6.8 (8.6)	5.4 (7.8)	6.7 (8.8)
Moderate/severe nose symptoms, No. (%)	75 (87.2)	328 (93.4)	359 (94.0)	178 (87.3)	953 (92.0)
Moderate/severe eye symptoms, No. (%)	68 (79.1)	266 (75.8)	274 (71.7)	99 (48.5)	715 (69.0)
Asthma, No. (%)	27 (31.4)	117 (33.3)	101 (26.4)	51 (25.0)	300 (29.0)
History of immunotherapy, %	37.2	39.9	29.8	29.4	34.3
Symptomatic medication in the last season/previous year, %	80.2	83.7	80.1	65.0	78.2

^aIncluding timothy (n=11) and mugwort (n=2).

Updosing with a maximum of 5 injections according to the recommended dose schedule was applied in 833 patients (80.4%); 1 additional injection was given to 136 patients (13.1%), 2 to 38 patients (3.7%) and more than 2 to 29 patients (2.8%). Antihistamine premedication prior to injections during updosing was used in 6.9% of patients.

Adverse Events

AEs were reported in 24.5% of the 1036 patients. The overall data for local and systemic reactions as well as for all adverse reactions are shown in detail in Table 2. The proportion of patients with AEs including adverse reactions and other AEs for the different allergens applied is shown

Table 2. Overview of All Local, Systemic and Adverse Reactions in 1036 Patients^a

	Local Reactions	Systemic Reactions	All Adverse Reactions
All reactions	164 (15.8) 588	100 (9.7) 237	230 (22.2) 825
During updosing	150 (14.5) 432	87 (8.4) 209	210 (20.3) 641
During maintenance	42 (4.4) 156	16 (1.7) 28	54 (5.7) 184
≤30 min after injection	71 (6.9) 237	23 (2.2) 55	88 (8.5) 292
>30 min after injection	82 (7.9) 312	64 (6.2) 150	124 (12.0) 462
Missing values	11 (1.1) 39	13 (1.3) 32	18 (1.7) 71
Unlikely causality	1 (0.1) 6	18 (1.7) 29	15 (1.4) 35
Possible causality	163 (15.7) 582	82 (7.9) 208	215 (20.8) 790
Intensity			
Mild	96 (9.3) 398	53 (5.1) 103	131 (12.6) 501
Moderate	46 (4.4) 144	31 (3.0) 95	69 (6.7) 239
Severe	22 (2.1) 42	15 (1.4) 35	30 (2.9) 77
Missing values	– 4	1 (0.1) 4	– 8
Treated by medication	41 (4.0) 100	48 (4.6) 119	77 (7.4) 219
Serious	–	6 (0.6) 39	6 (0.6) 39
Treatment terminated	9 (0.9) 12	17 (1.6) 52	23 (2.2) 64

^aData shown as No. (%) of patients and No. of events.

Table 3. Adverse Events (AEs) in Patients Treated With the Different Allergens Used in the Study^a

	Birch	Tree mix	Grass mix	Mite mix	All patients ^b
Patients treated, No.	86	351	382	204	1036
All AEs	23 (26.7) 67	77 (21.9) 202	104 (27.2) 382	47 (23.0) 194	254 (24.5) 869
Local reactions	16 (18.6) 42	47 (13.4) 126	74 (19.4) 290	25 (12.3) 121	164 (15.8) 588
Systemic reactions	9 (10.5) 17	27 (7.7) 59	38 (9.9) 82	24 (11.8) 64	100 (9.7) 237
Other AEs	3 (3.5) 8	10 (2.8) 17	8 (2.1) 10	6 (2.9) 9	27 (2.6) 44
Serious AEs	3 (3.5) 12	3 (0.9) 15	3 (0.8) 14	1 (0.5) 1	11 (1.1) 50
Termination due to AEs	3 (3.5) 9	11 (3.1) 32	9 (2.4) 21	7 (3.4) 17	31 (3.0) 81

^aData shown as No. (%) of patients and No. of events.

^bIncluding timothy (n=11) and mugwort (n=2).

in Table 3. The treatment was terminated due to AEs in 3.0% of patients. The majority of reactions were assessed to be causally related to the treatment. AEs were mild in 13.0% of patients, moderate in 8.1%, and severe in 3.2%; 8.5% of patients with AEs were treated with medication. AEs related to treatment and observed in 1% or more of patients are displayed in Figure 2. Local reactions at the injection site, such as swelling, erythema, and pruritus were reported with the highest frequency; systemic reactions were much less common, with dyspnea (1.2%), allergic rhinitis (1.0%), and pruritus (1.0%) as the most frequent reactions. The highest rates of local and systemic reactions were observed during up dosing at the dose of 3000 SQ+ and considerably lower rates were seen during maintenance therapy with 15 000 SQ+. Overall tolerability of treatment was assessed as good or very good by 94.9% of patients and 96.2% of physicians. Serious AEs were reported in 11 patients and were related to treatment in 6 of these. Of these 6 SAEs, 2 were classified as immediate reactions and 4 as delayed reactions. The immediate reactions were reported in a 51-year-old woman who developed tachycardia, hypotension, dyspnea, and chest tightness 2 minutes after the injection of a 6000 SQ+ dose and in an 18-year-old woman who experienced high blood pressure, generalized itching, and dizziness 10 minutes after the first injection (dose 300 SQ+); both reactions were related to tree mix and classified as medically important. The patients recovered after treatment with antihistamines and corticosteroids and discontinued treatment. Delayed reactions (1-5 hours after injection) were reported in 1 woman and 3 men who had been treated with birch, timothy grass, or grass mix (2 patients). They showed symptoms of facial swelling, edema, and urticaria in addition to breathing difficulties in 1 case (duration 2-3 hours, treatment continued) and bronchospasm and dyspnea in another (duration 12 hours, treatment discontinued). The dose was 3000 SQ+ in all cases. These patients visited a hospital acute day ward, recovered after treatment with antihistamines and corticosteroids, and were hospitalized overnight for observation. Adrenaline was not used in any of the patients with SAEs.

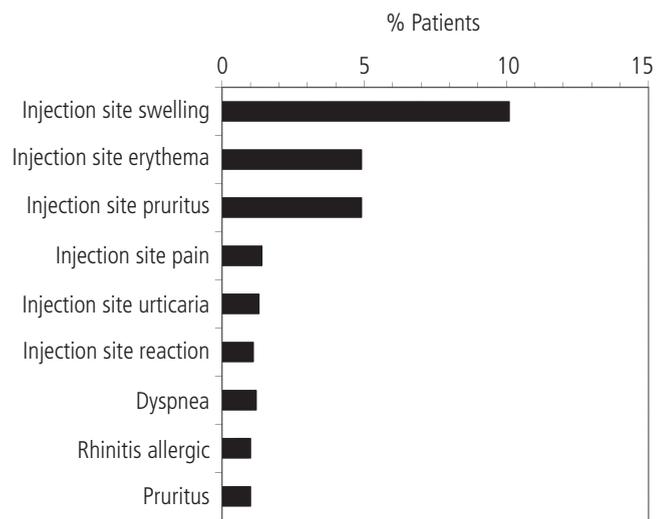


Figure 2. Percentage of patients with adverse events related to treatment (MedDRA Preferred Terms) observed in $\geq 1\%$ of patients for all patients documented, the total treatment period, and all allergens used.

Discussion

This study was initiated to evaluate tolerability with a new immunologically enhanced SCIT product with pollen and house dust mite allergens under real-life conditions. The prospective, open-label observational design was appropriate to record data on the routine use of SCIT in a real-life setting.

In the course of this study, data for routine application of a fast up dosed immunologically enhanced immunotherapy formulation with an optimized ratio of allergen and aluminium hydroxide as adjuvant (AVANZ) were recorded in 1036 patients treated with one of various pollen or house dust mite allergens. The study was started when the product became available in Germany as a Named Patient Product in September 2009 and, therefore, reflects the first systematically recorded data for the routine application of various allergens. Data from a previous controlled clinical trial in 400 patients treated with

5 injections for up dosing of 4-grass and rye allergens with weekly or 3-to-4 day intervals and 2 maintenance injections revealed significant immunologic effects and a favorable safety and tolerability profile [6].

The severity of symptoms in the patients in our study was assessed according to 'marked symptoms with mild interference with daily activities' as the criterion for moderate and 'unacceptable symptoms that considerably interfered with daily activities' as the criterion for severe symptoms. According to these criteria, 92.0% of all the patients treated had moderate to severe nasal symptoms (birch, 87.2%; tree mix, 93.5%; grass mix, 94.0%; mite mix, 87.2%). Moderate to severe eye symptoms were recorded in 69.0% of the patients (birch, 79.1%; tree mix, 75.7%; grass mix, 71.7%; mite mix, 48.5). Use of symptomatic medication in the previous season or previous year was reported in 78.2% of the patients (birch, 80.2%; tree mix, 83.7%; grass mix, 80.1%; mite mix, 65.0%) and thus appears to be low when compared with the percentage of patients who were assessed as having moderate to severe rhinoconjunctivitis symptoms, ie, patients treated with mite allergens. Due to the noninterventional design of our study, patients were not selected according to inclusion and exclusion criteria for the severity of rhinoconjunctivitis symptoms and use of symptomatic medication, but were treated at the discretion of the physician, reflecting the current practice for the use of SCIT in Germany. The characteristics of patients treated with grass mix in our study are similar to those reported in another large noninterventional, observational study with SCIT in patients allergic to grass pollen conducted in Germany [12]. During the observation period of our study, patients were treated for approximately 8 months and received a median of 11 injections. The recommended dosage schedule of 5 injections was followed in the majority of patients (80.4%). Data for maintenance treatment were available for more than 90% of the patients treated initially.

The application of the SCIT injections was generally well tolerated. AEs were reported in 24.5% of all patients treated throughout the observation period; the frequency was highest during up dosing and was considerably lower during maintenance therapy. The most frequent AEs were mild to moderate local reactions such as swelling and erythema at the injection site (in 15.8% of patients). Less frequent AEs related to treatment were systemic reactions, seen in 7.9% of patients; the most common of these were dyspnea (1.2% of patients), allergic rhinitis (1.0%), and pruritus (1.0%). The highest frequency of local reactions was reported for grass mix (19.4% of patients) and lower frequencies were seen for mite mix (12.3%) and tree mix (13.4%). Systemic reactions were observed with mite mix in 11.8% of patients and with birch in 10.5%, grass mix in 9.9% and tree mix in 7.7% of patients. In the controlled trial in which 201 patients had been treated with grass mix at weekly intervals during up dosing, local reactions were recorded in 36% of patients and systemic reactions in 21%. As to be expected for a noninterventional, observational study, lower rates of local and systemic reactions were reported during routine use of the product than in the controlled clinical trial. Similarly to in the trial, delayed reactions (local and systemic reactions >30 minutes after injection) were also more common than immediate reactions in

our study (12% vs 8.5%). Most systemic reactions were rated as mild (5.1%) or moderate (3.0%); they were severe in 1.4% of patients and treatment was discontinued in 1.6% of patients. Therefore, overall tolerability does not seem to be affected by the occurrence of delayed reactions given that severe reactions were only observed in a few patients. SAEs related to treatment were recorded in 6 (0.6%) of the 1036 patients; they were immediate reactions in 2 cases and delayed reactions in 4. Patients with delayed reactions were hospitalized overnight for observation in 4 cases and treatment was continued in 3 cases and discontinued in 1. Local and systemic reactions were most frequently reported for the third injection of the up dosing schedule (dose 3000 SQ+). Depending on the severity of the reaction it is recommended to repeat the last dose or reduce the dose by 1 to 3 steps in the dosage schedule. Good or very good overall tolerability assessments by patients and physicians were obtained for about 95% of patients. The pattern of AEs observed in our study was in line with patterns reported in the controlled trial with the same product [6] and previous trials using non-modified aluminium hydroxide-adsorbed grass pollen allergens [15,16]. In the randomized controlled clinical trial significant immunologic effects from the induction of immunoglobulin (Ig) G4 antibodies and IgE-blocking factor as a functional assay of serum IgG-associated inhibitory activity have been detected [6]. In a recent analysis of immunologic data from the trial published by Frew et al [15], a modest but significant inverse relationship was demonstrated between postimmunotherapy serum inhibitory activity and combined symptom-rescue medication scores. However, this has not been observed for immune reactive IgG4 levels [17], suggesting that an increase in IgE-blocking factor may predict clinical efficacy.

In conclusion, in this noninterventional, open-label, observational study, therapy with various pollen and mite allergens of the new hypoallergenic fast up dosed product with an optimized ratio of allergen and aluminium hydroxide as adjuvant was observed to be well tolerated in a large number of patients during routine treatment, although a number of patients experienced predominantly mild to moderate delayed systemic reactions.

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Conflicts of Interest

B Hauswald received remuneration from ALK for the documentation of patient data from her clinic for this study and has also received speakers' fees from ALK. F Becker and S Becker received remuneration from ALK for the documentation of patient data from their clinic for this study. J Schnitker is Managing and Scientific Director of the clinical research organization IAS GmbH, which was funded from ALK for this study. H Wolf and E Wüstenberg are employees of ALK.

Previous Presentation

Wolf H, Becker F, Becker S, Schnitker J, Wüstenberg E. Immuntherapie mit einem schnell aufdosierten hypoallergenem SCIT-Präparat: Verträglichkeit der Aufdosierung und der Erhaltungstherapie während der Routineanwendung. *Allergo J* 2011;20:S44-45. (Poster presentation at the 6th German Allergy Congress, 08 to 10 September 2011 Wiesbaden, Germany); Wolf H, Becker F, Becker S, Schnitker J, Wüstenberg E. Immunotherapy with a fast up-dosed immunologically enhanced SCIT preparation: tolerability of up-dosing and maintenance treatment during routine application. *Allergy* 2012;67(Suppl. 96):616-17. (Poster presentation at the 31th EAACI-Congress, 16 to 20 June 2012, Geneva, Switzerland).

References

- Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, Barlan IB. Clinical efficacy and immunologic mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. *Clin Exp Allergy*. 2010;40:922-32.
- Bousquet J, Lockey RF, Malling HJ. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy*. 1998;53:1-42.
- Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, Helms PJ, Hunt J, Liu N, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FER, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy*. 2008;63:5-34.
- Walker SM, Durham RS, Till SJ, Roberts G, Corrigan CJ, Leech SC, Krishna MT, Rajakulasingham RK, Williams A, Chantrell J, Dixon L, Frew AJ, Nasser SM. Immunotherapy for allergic rhinitis. *Clinical & Experimental Allergy*. 2011;41:1177-200.
- Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007; CD001936.
- Pfaar O, Jung K, Wolf H, Decot E, Kleine-Tebbe J, Klimek L, Wüstenberg E. Immunological effects and tolerability of a new fast uposed immunologically enhanced subcutaneous immunotherapy formulation with optimized allergen/adjutant ratio. *Allergy*. 2012;67:630-37.
- Li H, Nookala S, Re F. Aluminium hydroxide adjuvants activate caspase-1 and induce IL-1beta and IL-18 release. *J Immunol*. 2007;178:5271-6.
- Eisenbarth SC, Colegio OR, O'Connor W, Sutterwala FS, Flavell RA. Crucial role for the Nalp3 inflammasome in the immunostimulatory properties of aluminium adjuvants. *Nature*. 2008;453:1122-6.
- Kool M, Soullie T, van Nijmegen M, Willart MAM, Muskens F, Jung S, Hoogsteden HC, Hammad H, Lambrecht BN. Alum adjuvant boosts adaptive immunity by inducing uric acid and activating inflammatory dendritic cells. *J Exp Med*. 2008;205:869-82.
- Lambrecht BN, Kool M, Willaart MA, Hammad H. Mechanism of action of clinically approved adjuvants. *Curr Opin Immunol*. 2009;21:23-9.
- Rask C, Lund L, Lund G, Heydenreich B, Wurtzen P, Bellinghausen I, Saloga J, Lund K. An alternative allergen:adjuvant formulation potentiates the immunogenicity and reduces the allergenicity of a novel subcutaneous immunotherapy product for treatment of grass pollen allergy. *Clin Exp Allergy*. 2012(42):1356-68.
- Bergmann KC, Wolf H, Schnitker J, Petermann F. Quality of life and compliance of patients treated with specific immunotherapy using grass and rye allergens (LQC study). *Allergo J*. 2000;9:480-8.
- Sundin B, Lilja G, Graff Lonnevig V, Hedlin G, Heilborn H, Norrland K, Pegelow KO, Löwenstein H. Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma. *J Allergy Clin Immunol*. 1986;77(3):478-87.
- Aas K, Backman A, Belin L, Weeke B. Standardization of allergen extracts with appropriate methods. The combined use of skin prick testing and radio-allergosorbent tests. *Allergy*. 1978;33(3):130-7.
- Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006 Feb;117(2):319-25.
- Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, Ring J, Effendy I, Behrendt W, Frosch PJ, Przybilla B, Brunner FX, Merk HF, Kapp A, Schnitker J, Wolf H. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunol*. 1997;100(1):23-9.
- Shamji MH, Ljørring C, Francis JN, Calderon MA, Larche M, Kimber I, Frew AJ, Ipsen H, Lund K, Würtzen PA, Durham SR. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. *Allergy*. 2011;67:217-26.

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